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STUDIES IN CALCIUM AND PHOSPHORUS METABOLISM¹

PART IV

THE INFLUENCE OF FREE FATTY ACIDS IN THE INTESTINE
ON THE ABSORPTION AND EXCRETION OF THE MINERAL
ELEMENTS

BY S. V. TELFER

(From the Institute of Physiology, University of Glasgow)

Introduction.

IN the first of the present series of studies (1) it was shown that one of the important factors influencing the mode of excretion of calcium and phosphorus is the concentration of fatty acids in the intestinal contents. Defective absorption of fat, unaccompanied by any serious defect in fat-splitting, was found to be associated with a specific alteration in the normal distribution of lime and phosphoric acid in the urine and faeces. A brief reference to the earlier work may serve to recall the salient features of this change in the excretion of the mineral elements.

In healthy children on a diet of cow's milk the faecal solids contain from 20 to 25 per cent. of mineral matter, which consists almost entirely of lime, magnesia, and phosphoric acid. The lime value is generally from 8.0 to 10.0 per cent., the magnesia a little over 1.0 per cent. The percentage of phosphoric acid is more variable and depends chiefly on the proportion of lime combined with fatty acids as insoluble soaps. Generally, it lies between 6.0 and 9.0 per cent.

The total fatty derivatives constitute approximately one-third of the faecal solids (30-40 per cent.). Only a small amount of neutral fat, usually less than 5.0 per cent., escapes unsplit in the faeces. The remainder of the fatty derivatives consists of free and combined fatty acids in variable proportions. The percentage of combined fatty acids is of importance as it affords an index of the amount of lime eliminated in the faeces as insoluble soaps. The lime equivalent of the latter is approximately one-tenth of the combined fatty acids. Of the total lime eliminated by the bowel 20-30 per cent. commonly exists in the form of soaps, the remainder as phosphate.

¹ Received June 18, 1926.

The urinary calcium is usually an almost negligible proportion (1-2 per cent.) of the total amount eliminated. The urinary magnesium is more variable, perhaps on account of the greater solubility of its salts and the smaller intake, but it is always much less than the output in the faeces. The urinary phosphorus is generally slightly less than the faecal phosphorus.

The weight of dried faeces estimated over an extended period varies but little in the same individual on such a uniform diet as cow's milk. Within limits it is proportional to the output of calcium in the faeces, the percentage of lime tending to remain constant. An increased output of lime in the faeces, following defective utilization of calcium, may therefore give rise to a high faecal weight without any marked alteration in the percentage value of lime in the faecal solids. Conversely, an increased utilization of calcium may be expressed by a fall in the faecal weight, the composition of the faecal solids showing but little alteration.

When fat absorption is defective the increased concentration of fatty acids in the intestine appears to facilitate the combination of calcium with fatty acids and to lessen the formation of phosphate of lime. The faecal solids contain not only an excess of fatty derivatives but a greater proportion of the calcium in the form of insoluble soaps with a corresponding reduction of the calcium existing as phosphate of lime. The percentage value of fatty derivatives in the faecal solids, and particularly that of *combined* fatty acids, is increased. The percentage of total mineral matter is reduced and that of the individual mineral constituents, the lime, magnesia, and phosphoric acid. The reduction of phosphoric acid is greater than that of the lime and magnesia owing to the increased linkage of calcium with fatty acids to form insoluble soaps and the lessened restriction of phosphoric acid to the intestine as phosphate of lime. The lime-phosphoric acid ratio of the faecal solids is therefore increased, the percentage value of phosphoric acid falling as that of combined fatty acids rises. The stools are bulky and of a pasty consistency. The weight of dried faeces per diem is considerably increased by the elimination of the excess of fatty derivatives.

The alteration of the calcium combinations in the intestinal contents is reflected in the distribution of phosphorus in the urine and faeces. The output of urinary phosphorus is raised at the expense of the faecal phosphorus, and the degree of deviation of phosphoric acid from the intestine to the urine is roughly proportional to the increase of fatty derivatives in the faecal solids. In extreme cases, as for example in jaundice (2), in which the fatty derivatives may be as high as 80 per cent. of the faecal solids, the phosphorus excreted by the urine may be more than three times the faecal output. The urinary calcium is slightly increased, probably as a result of the excessive elimination of the phosphoric acid radical by the kidney.

These observations led to the important conclusion that the conditions which permit of a persistent excess of free fatty acids in the intestine facilitate the absorption of phosphorus.

Present Investigation.

The changes in excretion described above were observed by the writer in 1921 in cases of congenital atresia of the bile-ducts (2). Recently in a case of catarrhal jaundice in a child an excellent opportunity was afforded of confirming and extending these observations. A study of mineral metabolism was made at three different periods in the course of the illness:

(i) When bile was absent from the intestine and fat absorption was most defective.

(ii) After partial recovery, the faeces still containing an appreciable excess of fatty derivatives.

(iii) Near complete recovery, when the normal absorption of fat had been re-established.

In this way data were obtained which permitted of a comparison of the mode of excretion of the mineral elements at three widely different levels of fatty acid concentration in the intestine in the same individual.

Methods.

Throughout the illness the child was maintained on a diet consisting of 1,400 c.c. of fresh cow's milk daily. The intakes of fat and mineral matter were therefore uniform during the three experimental periods. The urine and faeces corresponding to each period of four days were collected separately and quantitatively. The faeces were dried on a water-bath to constant weight, finely ground, mixed, and preserved in air-tight bottles. The urine was acidified with nitric acid and diluted to a known volume. The excreta were then subjected to the routine chemical examination adopted in these studies, the various estimations of lime, magnesia, phosphoric acid, and fatty derivatives being made by the ordinary analytical methods.

The results are recorded in the table on p. 4.

Discussion.

In healthy infants more than 90 per cent. of the fat intake is absorbed. The absorption of fat was reduced to 70.3 per cent. in Period I, when bile was excluded from the gut and a large excess of fatty derivatives above the normal was present in the intestine. A fortnight later, when bile was only partly excluded (Period II), absorption had increased to 87.5 per cent., so that the concentration of fatty derivatives in the gut was considerably diminished. At the end of four weeks (Period III), when bile was again freely entering the intestine, the normal level in fat absorption was almost regained (90.8 per cent.).

The analytical data during the first period afford a typical illustration of excretion in jaundice. The high faecal weight and concentration of fatty derivatives in the faecal solids were associated with an excessive formation

of calcium soaps, as indicated by the combined fatty acids (38.7 per cent.). The percentage values of total mineral matter, lime, and magnesia were reduced to about half the average level by fat 'dilution'. Correlated with the increased linkage of calcium with fatty acids to form insoluble soaps, the percentage of lime in the faeces was more than double that of phosphoric acid and the urinary phosphorus about three and a half times greater than the faecal phosphorus. The absorption of phosphorus was therefore excessively great during this period.

A. C. Female. Aged 3½ years. 11.3 kilos.

Diet: 1,400 c.c. cow's milk daily.

	Period I.	Period II.	Period III.
Fat absorption (per cent.)	70.3	87.5	90.8

Distribution of Mineral Elements in Excreta (4 days).

	CaO.	MgO.	P ₂ O ₅ .	CaO.	MgO.	P ₂ O ₅ .	CaO.	MgO.	P ₂ O ₅ .
	gr.	gr.	gr.	gr.	gr.	gr.	gr.	gr.	gr.
Urine	0.31 = 6.8 %	0.14 = 24.1 %	6.37 = 77.2 %	0.22 = 4.7 %	0.09 = 17.6 %	3.34 = 44.4 %	0.1 = 1.5 %	0.09 = 11.7 %	2.39 = 25.9 %
Faeces	4.27 = 93.2 %	0.44 = 75.9 %	1.87 = 22.8 %	4.42 = 95.3 %	0.42 = 82.4 %	4.24 = 55.6 %	6.53 = 98.5 %	0.68 = 88.3 %	6.81 = 74.1 %

Analysis of Faecal Solids (per cent.).

Mineral matter	14.0	25.2	39.2
Lime (CaO)	6.5	10.6	16.3
Magnesia (MgO)	0.63	1.02	1.72
Phosphoric acid (P ₂ O ₅)	2.65	10.17	16.99
Neutral fat	6.83	2.7	2.87
Free fatty acids	25.07	20.55	24.38
Combined fatty acids	38.7	27.16	10.95
Total fat	70.6	50.41	38.2
Percentage CaO as soaps of total CaO	60.6	26.1	6.7
Urinary phosphorus	3.4	1	1
Faecal phosphorus	1	1.2	2.9
Faecal weight (dry)	70.7 grm.	41.7 grm.	40.1 grm.

The mode of excretion of the mineral elements in Periods II and III is in striking contrast with that of the first period. With the disappearance of the excess of fatty derivatives from the intestinal contents the faecal weight fell and the concentration of mineral matter in the faecal solids increased. The urinary lime and magnesia relatively to their faecal outputs were diminished, but the most notable alteration occurred in the distribution of the phosphorus. A pronounced fall in the urinary phosphorus was accompanied by a corresponding rise in the faecal phosphorus. Further, the rise in the percentage of phosphoric acid in the faecal solids was much greater than that of the lime and magnesia, indicating that the increased faecal output of phosphorus was due to its restriction

to the intestine chiefly as phosphate of lime. (3) In Period III almost a complete reversal in the ratio of urinary to faecal phosphorus found in the initial period had been effected. The fall in the percentage value of combined fatty acids from 38.7 per cent. in Period I, to 27.16 per cent. in Period II, and 10.95 per cent. in Period III shows that calcium soap formation in the intestine was progressively reduced. The reduction in soap formation was obviously related to the increased elimination of phosphorus as phosphate of lime in the faeces, and the fall in urinary phosphorus.

The absorption of phosphorus was therefore greatest in Period I, less in Period II, and least in Period III, the differences being of considerable magnitude and corresponding to the degree of displacement of phosphoric acid from combination with calcium in the intestine by fatty acids.

This relationship between the absorption of phosphorus and the calcium combinations which are effected in the gut would appear to be of importance in dietetics. The intestinal conditions which permit of the linkage of calcium with fatty acids are clearly antagonistic to the restriction of phosphorus as phosphate of lime to the intestine, and hence to defective absorption of this element. It will be shown later (Part V) that cod-liver oil possesses the property of inducing these conditions in remarkable degree, when administered in the active stage of infantile rickets.

The interpretation of the data with regard to the influence of the persistent excess of fatty acids in the intestine on the absorption of calcium and magnesium is more difficult. Studies by Grosser (4) and others have shown that when solutions of lime salts are injected intravenously the calcium is rapidly eliminated from the blood, not by the urine, but mainly into the intestine, whence it escapes in the faeces. The same process might be held to operate if an excess of calcium above requirements were absorbed directly from the intestine; the increase in urinary calcium, if any, would not be commensurate with the increased absorption.

In Period I, when the fatty acid concentration in the intestine was greatest, the urinary outputs of calcium and magnesium relatively to the faecal outputs were slightly but definitely increased, which suggests that some rise in the absorption of these elements had occurred. It is impossible, however, for the reasons given above, to determine from the data alone whether this increased absorption was of significant proportions or not. A large excess of phosphoric acid was in process of elimination at the same time, and the small rise in the urinary excretion of the basic elements may have been dependent on the increased transport of the acid radical through the kidney.

The importance of the reaction of the intestinal contents in controlling the absorption of the mineral elements has been referred to in a previous study (3). Recently Irving and Ferguson (5) working on dogs and rabbits have found that the rate of absorption of calcium from solutions of calcium chloride introduced directly into the intestine is very much increased by raising the hydrogen-ion concentration of the solutions.

In Period I the alkaline bile was absent from the intestine and the concentration of fatty acids was highest; in the last period the outflow of bile was re-established and the excess of fatty acids had almost disappeared. The degree of acidity of the intestinal contents might therefore have been appreciably greater in the first than in the last period; but since measurements of the hydrogen-ion concentration of the intestinal contents can only be carried out on animals the extent to which this factor varied and influenced absorption of the mineral elements in each period is unknown.

The results presented here are in complete agreement with the observations made in former studies, and afford further illustration of the wide differences which may occur in the absorption and excretion of ingested mineral matter with a variation in the concentration of fatty acids in the intestine.

In the communication on mineral metabolism in infantile rickets which follows (Part V), it will be shown that the composition of the faecal solids and the distribution of the mineral elements during the active stage of the illness are almost identical with those found in Period III, while in healing rickets after the administration of cod-liver oil, the mode of excretion acquires the characteristics of the first period. The importance of elucidating the factors which determine these two modes of excretion is evident.

The data are also of interest clinically since they show quantitatively the changes in excretion which occur with recovery of the hepatic function. These changes are very extensive; and, as they are recognizable before any marked alteration takes place in the physical condition of the subject, the scheme of analysis by which they were followed may be recommended for clinical consideration.

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STUDIES IN CALCIUM AND PHOSPHORUS METABOLISM ¹

PART V

INFANTILE RICKETS. THE EXCRETION AND ABSORPTION OF THE MINERAL ELEMENTS AND THE INFLUENCE OF FATS IN THE DIET ON MINERAL ABSORPTION

By S. V. TELFER

(From the Institute of Physiology, University of Glasgow)

IN a previous study of calcium and phosphorus metabolism in children on a diet of cow's milk, it was found that the retentions of lime and phosphoric acid were approximately equal in normal subjects, the values ranging from 0.06 grm. to 0.12 grm. per kilo of body-weight per day (1). The retentions were shown to be diminished in infantile rickets. The conditions which might give rise to the faulty utilization of the two bone-forming elements so characteristic of the disease were discussed at some length, and the view was expressed that the most feasible explanation for the low retentions during the active stage of the illness was defective absorption of calcium, possibly secondary to some alteration in the gastro-intestinal functions.

During the past year further inquiry has been made to ascertain whether the mode of excretion of the mineral elements in infantile rickets differs appreciably from the normal and is in harmony with this explanation. The results of this work are discussed in the present communication.

Method of Investigation.

Cases of early rickets were selected. In each of these the distribution of the mineral elements in the urine and faeces and the composition of the faecal solids were determined. The data so obtained were compared with similar data derived from previous work (2) on excretion in normal subjects (see p. 1, Part IV).

The opportunity was then taken of studying the effects of various fats, and particularly of cod-liver oil, on the excretion and absorption of the mineral elements during the active stage of the disease.

The method of procedure has already been described (1). After a pre-period of three days on a fixed intake of fresh undiluted cow's milk sweetened with cane

¹ Received June 18, 1926.

sugar, each subject was placed on a 'metabolism' bed and the urine and faeces collected separately and quantitatively over a period of seven days. The excreta were then subjected to the routine chemical examination adopted in these studies. The retentions of lime, magnesia, and phosphoric acid were calculated from the difference between the amounts ingested and excreted during the seven-day period. At the end of this period the fat to be examined was added to the diet, which was otherwise unaltered. After a pre-period of three days the subject was again placed on the 'metabolism' bed for seven days, and the excreta collected and examined as before. The effects of the added fat on the retentions and mode of excretion of the mineral elements were ascertained by comparing the two sets of data. Cod-liver oil was first used, then olive oil, butter fat, and human milk fat. The last was extracted from twenty litres of human milk collected at the Royal Maternity Hospital, Glasgow, and the Barshaw Hospital for Women, Paisley. The results are presented in the following tables:

Case I. O. G. Aged $1\frac{2}{3}$ years.

Period I (7 days).

Period II (7 days).

(Active Rickets.)

(Cod-liver Oil)

Retention of Mineral Elements (grm.).

	CaO.	MgO.	P ₂ O ₅ .	CaO.	MgO.	P ₂ O ₅ .
Intake (grm.)	11.48	—	15.05	11.48	1.61	15.75
Output "	8.53	—	10.72	6.55	1.01	10.95
	<u>2.95</u>	—	<u>4.33</u>	<u>4.93</u>	<u>0.60</u>	<u>4.80</u>
Retention per kilo per day	0.05	—	0.07	0.08	0.009	0.08

Distribution of CaO, MgO, P₂O₅ in Excreta (7 days).

	CaO.	MgO.	P ₂ O ₅ .	CaO.	MgO.	P ₂ O ₅ .
Urine	0.12	—	3.94	0.10	0.19	6.63
Faeces	8.41	—	6.78	6.45	0.82	4.32
Total	<u>8.53</u>	—	<u>10.72</u>	<u>6.55</u>	<u>1.01</u>	<u>10.95</u>

Analysis of Faecal Solids (per cent.).

Total mineral matter	37.34	26.44
Lime (CaO)	17.60	12.60
Magnesia (MgO)	1.99	1.6
Phosphoric acid (P ₂ O ₅)	14.20	8.44
Neutral fat	5.27	5.09
Free fatty acids	5.48	7.26
Combined fatty acids	25.15	30.40
Total fat	<u>35.90</u>	<u>42.75</u>
Percentage of CaO as soaps of total CaO	14.5	24.6
Urinary phosphorus	1	1.5
Faecal phosphorus	<u>1.7</u>	<u>1</u>
Faecal weight	47.8 grm.	51.2 grm.

Case I. Period I. (Active rickets.) The defective utilization of the mineral elements characteristic of the active stages of the disease is shown by the low retention of lime and phosphoric acid. Almost the whole of the lime excreted appeared in the faeces (98.6 per cent.). The percentage values of total mineral matter (37.34) and of the individual mineral constituents, the lime, magnesia, and associated phosphate, were all excessively high. The percentage of total fatty derivatives was within normal limits.

The lime existing as soaps calculated from the combined fatty acids was only 14.5 per cent. of the total lime of the faeces. A very large proportion of the calcium was therefore eliminated by the bowel in combination with phosphoric acid. The excessive restriction of phosphorus to the intestine is also indicated by the low ratio of urinary to faecal phosphorus ($\frac{1}{1.7}$) and the high percentage value of phosphoric acid (14.2) in the faecal solids relatively to the lime (17.6).

The composition of the faecal solids and the distribution of the mineral elements in the urine and faeces clearly show that the low retentions of lime and phosphoric acid were associated with an increased elimination of mineral matter in the faeces, which consisted mainly of phosphate of lime.

Period II. (Cod-liver oil.) The effects of the cod-liver oil administration are easily followed. An increase in the retention values of the mineral elements immediately occurred, with well-marked alterations in the distribution of the mineral elements in the excreta and the composition of the faecal solids.

Owing to the increased retention of calcium, much less lime was eliminated in the faeces. The output of calcium by the urine was practically unaffected. A profound change occurred in the excretion of the phosphorus, the urinary output so far exceeding the faecal output that the ratio of urinary to faecal phosphorus of Period I was almost inverted ($\frac{1.5}{1}$).

The analysis of the faecal solids showed striking changes, the most outstanding being the reduction in the concentration of mineral matter from 37.34 to 26.44 per cent., with a corresponding fall in the percentage values of lime and magnesia. An important feature in the reduction of the mineral concentration of the faecal solids is the much greater fall in the percentage value of phosphoric acid than that of the lime. This is obviously correlated with the greater output of urinary phosphorus and an increased formation of calcium soaps in the intestine. Of the total lime of the faeces 24.6 per cent. existed as soaps, the increase in fatty derivatives being due mainly to combined fatty acids.

No significant change occurred in the faecal weight.

Case II. Period I. (Active rickets.) The retentions of the mineral elements were below the normal, that of magnesia being slightly on the negative side. No significance was attached to the negative value of this retention, which is small enough to be within the range of experimental error.

A minute amount of calcium was present in the urine, which also contained only a small fraction of the total magnesium excreted. The urinary phosphorus was exceptionally low, 77.6 per cent. of the total amount eliminated being found in the faeces.

A. The stools were loose during the metabolic period, and consequently an excess of fatty derivatives escaped in the faeces. The concentration of mineral matter in the faecal solids (21.8 per cent.), though apparently within normal limits, was therefore relatively high. The fatty derivatives formed approximately one-half of the faecal solids (49.74 per cent.), so that the mineral component of the faeces had undergone considerable fat 'dilution'.

The faecal weight (181.8 gm.) was excessively high.

The low percentage of combined fatty acids showed that only a very small proportion of the total lime of the faeces existed as soaps (12.0 per cent.). The

outstanding feature of excretion in this, as in the previous case, was therefore an excessive loss of calcium from the bowel mainly as phosphate of lime.

B. A second analysis of the faecal solids was made after the stools had become normal in consistency. The data show that the concentration of mineral matter in the faecal solids (32.88 per cent.) was appreciably greater than the normal when the total fatty derivatives were reduced to 37.75 per cent. A very low value for combined fatty acids (5.45 per cent.) was again found.

Case II. A. V. Aged $1\frac{4}{12}$ years.

Period I (7 days).

(Active Rickets.)

Period II (6 days).

(Cod-liver Oil.)

Retention of Mineral Elements (grm.).

	CaO.	MgO.	P ₂ O ₅ .	CaO.	MgO.	P ₂ O ₅ .
Intake	12.95	1.61	15.05	9.60	1.38	13.5
Output	12.76	1.63	14.52	2.73	0.75	7.77
	<u>0.19</u>	<u>- 0.02</u>	<u>0.53</u>	<u>6.87</u>	<u>0.63</u>	<u>5.73</u>
Retention per kilo per day	0.027	- 0.002	0.075	0.14	0.01	0.12

Distribution of CaO, MgO, P₂O₅ in Excreta (7 days).

	CaO.	MgO.	P ₂ O ₅ .	CaO.	MgO.	P ₂ O ₅ .
Urine	0.03	0.07	3.36	0.12	0.24	6.89
Faeces	12.73	1.56	11.16	2.61	0.51	1.88
Total	<u>12.76</u>	<u>1.63</u>	<u>14.52</u>	<u>2.73</u>	<u>0.75</u>	<u>7.77</u>

Analysis of Faecal Solids (per cent.).

	(A)	(B)	
Total mineral matter ...	21.8	32.88	17.08
CaO ...	7.0	12.0	6.5
MgO ...	0.86	1.26	1.27
P ₂ O ₅ ...	6.14	12.7	3.45
Neutral fat ...	11.56	4.36	13.44
Free fatty acids ...	29.86	27.94	13.06
Combined fatty acids ...	8.32	5.45	27.4
Total fat ...	<u>49.74</u>	<u>37.75</u>	<u>53.9</u>
Percentage of CaO as soaps of total CaO ...	12.0		42.9
Urinary phosphorus ...	1		4.6
Faecal phosphorus ...	3.4		1
Faecal weight ...	181.8 grm.		46.9 grm.

Period II. (Cod-liver oil.) In order to render the effects produced by the cod-liver oil as clearly evident as possible, the moderate dose administered in the preceding case was doubled. The retentions of lime, magnesia, and phosphoric acid were immediately raised to a high level. The urinary outputs of lime and magnesia were increased, the latter very considerably. A striking alteration was effected in the excretion of phosphorus, 82.3 per cent. being eliminated in the urine. The ratio of urinary to faecal phosphorus was changed from $\frac{1}{3.4}$ to $\frac{4.6}{1}$.

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The alteration in the composition of the faecal solids was similar to that observed in the previous case. The concentration of mineral matter was reduced below the normal level. This was due in part to 'fat dilution', since the percentage value of total fatty derivatives (53.9) was considerably increased, and partly to the disappearance of the excess of phosphate of lime from the intestine, as a result of the increased utilization of calcium and phosphorus. The reduction in the percentage value of phosphoric acid to about half that of the lime and the great rise in combined fatty acids indicated that calcium soap formation had increased at the expense of the phosphate. The calculated proportion of lime existing as soaps (42.9 per cent.) shows that nearly half the total calcium eliminated in the faeces had undergone this transformation.

The faecal weight was much reduced.

Case III. G. B. Aged 2½ years.

	Period I (7 days). (Healing Rickets.)			Period II (7 days). (Cod-liver Oil.)		
	<i>Retention of Mineral Elements (gram.).</i>					
	CaO.	MgO.	P ₂ O ₅ .	CaO.	MgO.	P ₂ O ₅ .
Intake	17.22	2.28	22.54	17.22	2.28	23.59
Output	10.57	1.42	16.42	9.47	1.65	16.20
	<u>6.65</u>	<u>0.86</u>	<u>6.12</u>	<u>7.75</u>	<u>0.63</u>	<u>7.39</u>
Retention per kilo per day	0.09	0.01	0.08	0.11	0.009	0.10

Distribution of CaO, MgO, P₂O₅ in Excreta (7 days).

	CaO.	MgO.	P ₂ O ₅ .	CaO.	MgO.	P ₂ O ₅ .
Urine	0.07	0.37	9.52	0.35	0.51	10.71
Faeces	10.5	1.05	6.9	9.12	1.14	5.49
Total	10.57	1.42	16.42	9.47	1.65	16.20

Analysis of Faecal Solids (per cent.).

Total mineral matter	27.54	25.5
CaO	14.0	12.8
MgO	1.4	1.6
P ₂ O ₅	9.15	7.7
Neutral fat	4.08	4.67
Free fatty acids	3.42	4.38
Combined fatty acids	36.75	35.9
Total fat	44.25	44.95
Percentage of CaO as soaps of total CaO	26.7	28.6
Urinary phosphorus	1.4	1.9
Faecal phosphorus	1	1
Faecal weight	75.5 gm.	71.3 gm.

Case III. Period I. (Healing rickets.) The subject of this study was selected as a typical example of infantile rickets, the diagnosis apparently being confirmed clinically by X-ray examination. The mode of excretion determined by the quantitative examination of the urine and faeces was so widely different from that previously found in the acute stages of the disease, that doubt was at once entertained regarding the diagnosis, or rather the phase, of the illness.

The retentions of lime, magnesia, and phosphoric acid were at a high level. The urinary phosphorus was considerably in excess of the faecal phosphorus, while the concentration of mineral matter in the faecal solids (27.54 per cent.) was almost within normal limits. Finally, the high percentage value of combined fatty acids (36.75) with the excess of urinary over faecal phosphorus ($\frac{1.4}{1}$) indicated the presence of a considerable proportion of calcium as soaps in the faeces.

This strong resemblance to the mode of excretion of the mineral elements seen after treatment of infantile rickets with cod-liver oil, and illustrated by the two preceding examples, warranted the opinion that, despite the evidence from X-ray examination, the disease had passed spontaneously into a healing stage.

Subsequent X-ray photographs of the epiphyseal ends of the radius and ulna showed that healing was undoubtedly in progress.

Period II. (Cod-liver oil.) The effects of cod-liver oil administration were naturally less striking in this case. The retentions of lime and phosphoric acid were slightly augmented and the ratio of urinary to faecal phosphorus still further increased. A slight fall occurred in the concentration of mineral matter in the faecal solids and in the faecal weight. No significant change in the fatty derivatives was apparent, the high percentage value of combined fatty acids of the first period being maintained.

Case IV. J. McD. Aged $1\frac{9}{12}$ years.

	Period I (7 days). (Active Rickets.)			Period II (7 days). (Olive Oil.)			Period III (7 days). (Cod-liver Oil.)		
	<i>Retention of Mineral Elements (gram.).</i>								
	CaO.	MgO.	P ₂ O ₅ .	CaO.	MgO.	P ₂ O ₅ .	CaO.	MgO.	P ₂ O ₅ .
Intake	14.0	1.75	18.06	14.42	2.01	18.90	14.42	2.01	18.90
Output	11.44	1.40	14.75	13.90	1.62	18.05	8.37	1.30	13.83
	<u>2.56</u>	<u>0.35</u>	<u>3.31</u>	<u>0.52</u>	<u>0.39</u>	<u>0.85</u>	<u>6.05</u>	<u>0.71</u>	<u>5.07</u>
Retention per kilo per day	0.04	0.006	0.05	0.009	0.006	0.015	0.10	0.01	0.09
	<i>Distribution of CaO, MgO, P₂O₅ in Excreta (7 days).</i>								
	CaO.	MgO.	P ₂ O ₅ .	CaO.	MgO.	P ₂ O ₅ .	CaO.	MgO.	P ₂ O ₅ .
Urine	0.14	0.21	4.25	0.10	0.22	4.03	0.21	0.21	6.72
Faeces	11.30	1.19	10.50	13.80	1.40	14.02	8.16	1.09	7.11
Total	<u>11.44</u>	<u>1.40</u>	<u>14.75</u>	<u>13.90</u>	<u>1.62</u>	<u>18.05</u>	<u>8.37</u>	<u>1.30</u>	<u>13.83</u>
	<i>Analysis of Faecal Solids (per cent.).</i>								
Total mineral matter	43.32	34.3	33.3
CaO	17.05	13.35	14.1
MgO	1.8	1.36	1.89
P ₂ O ₅	15.84	13.56	12.23
Neutral fat	4.35	6.58	7.8
Free fatty acids	9.45	23.42	15.0
Combined fatty acids	17.85	15.12	24.35
Total fat	<u>31.65</u>	<u>45.12</u>	<u>47.15</u>
Percentage of CaO as soaps of total CaO	10.6	11.5	17.6
Urinary phosphorus	1	1	1
Faecal phosphorus	<u>2.4</u>	<u>3.4</u>	<u>1.06</u>
Faecal weight	66.3 gram.	103.4 gram.	57.9 gram.

Case IV. Period I. (Active rickets.) The characteristic low retentions were found in this case, that of phosphoric acid being appreciably greater than the lime. The urinary lime and magnesia constituted very small fractions of the total amounts excreted, while the urinary phosphorus was less than half the faecal phosphorus. The concentration of mineral matter in the faecal solids and the percentage value of the individual mineral constituent were all excessively high. The total fat was within the normal limits. The small proportion of lime existing as soaps calculated from the combined fatty acids together with the low ratio of urinary to faecal phosphorus indicated that most of the lime was eliminated by the bowel as phosphate.

Period II. (Olive oil.) In the second period olive oil was added to the diet. A fall in the retentions of lime and phosphoric acid resulted. The lime and phosphoric acid excreted by the bowel were considerably increased, while no significant change occurred in their urinary outputs. The urinary phosphorus was less than a third of the faecal phosphorus.

The concentration of mineral matter in the faecal solids was appreciably lowered, but the high percentage of fatty derivatives indicated that this was due to fat 'dilution'. The excessive elimination of the mineral elements by the bowel was in this period associated with a high faecal weight.

Period III. (Cod-liver oil.) The olive oil was replaced by cod-liver oil in order to obtain comparative data. The low retentions were immediately raised to the normal level. The urinary calcium was definitely increased, while the urinary output of phosphorus approached the faecal output. The increased retention of the mineral elements as a result of the cod-liver oil administration coincided, as in the preceding cases, with a diminished elimination of the latter by the bowel. The amount of phosphate excreted in the faeces during this period, for example, was nearly 7 grm. less than in the second period. The loss of nearly 1 grm. of phosphoric acid per day and 0.8 grm. of lime had been obviated.

No significant changes were observed in the concentration of mineral matter in the faecal solids. The percentage value of combined fatty acids was raised, the increased calcium soap formation, at the expense of the phosphate, being correlated with the rise in the ratio of urinary to faecal phosphorus.

The smaller elimination of the mineral elements in the faeces was associated with a pronounced fall in the faecal weight.

Case V. Period I. (Active rickets.) Diminished retention values of lime, magnesia, and phosphoric acid were found. The urinary phosphorus was less than the faecal phosphorus, but the difference between these was not so great as in previous cases. The concentration of mineral matter in the faecal solids was within normal limits, the excessive loss of the mineral elements in the faeces being associated with a high faecal weight (88.6 grm.). The percentage of total fatty derivatives was near the upper normal limit.

Period II. (Butter fat.) Butter fat was emulsified with the milk during the second period. The retentions were unaltered. Definite effects on the excretion of the mineral elements had, however, been produced. A slight rise in urinary magnesia occurred. The output of phosphorus by the urine was increased at the expense of the faecal phosphorus, the rise in the percentage of combined fatty acids of the faecal solids showing that this was related to increased calcium soap formation. As the output of lime in the faeces was the same in both periods, it is obvious that the increased elimination of calcium as soap by the bowel was balanced by a diminished output of calcium as phosphate.

The slight increase in the concentration of mineral matter in the faecal solids was associated with a definite fall in the faecal weight, so that no significant change occurred in the total amounts of mineral matter eliminated by the bowel.

Period III. (Cod-liver oil.) In the third period cod-liver oil was administered. The retentions of lime and phosphoric acid were doubled, the magnesia, however,

remaining unchanged. The outputs of lime and magnesia by the urine were definitely increased. A pronounced rise in the urinary excretion of phosphorus corresponding to a fall in the faecal output of this element was again a notable feature.

The percentage of combined fatty acids in the faecal solids was slightly increased above the high value found in the preceding period.

The concentration of mineral matter, previously within normal limits, was but little reduced, the diminished loss of the mineral elements in the faeces being associated with a marked fall in the faecal weight.

Case V. M. McD. Aged $\frac{10}{12}$ year.

	Period I. (Active Rickets.)			Period II. (Butter Fat.)			Period III. (Cod-liver Oil.)		
	<i>Retention of Mineral Elements (grm.).</i>								
	CaO.	MgO.	P ₂ O ₅ .	CaO.	MgO.	P ₂ O ₅ .	CaO.	MgO.	P ₂ O ₅ .
Intake	11.2	1.4	14.35	11.2	1.4	14.35	11.2	1.4	14.35
Output	9.04	1.2	12.64	9.0	1.25	12.6	7.06	1.26	10.54
	<u>2.16</u>	<u>0.2</u>	<u>1.71</u>	<u>2.2</u>	<u>0.15</u>	<u>1.75</u>	<u>4.14</u>	<u>0.14</u>	<u>3.81</u>
Retention per kilo per day	0.037	0.003	0.03	0.038	0.002	0.03	0.07	0.002	0.066

Distribution of CaO, MgO, P₂O₅ in Excreta (7 days).

	CaO.	MgO.	P ₂ O ₅ .	CaO.	MgO.	P ₂ O ₅ .	CaO.	MgO.	P ₂ O ₅ .
Urine	0.14	0.199	5.62	0.12	0.27	6.33	0.315	0.39	6.40
Faeces	8.90	1.01	7.02	8.88	0.98	6.27	6.75	0.89	4.14
Total	<u>9.04</u>	<u>1.20</u>	<u>12.64</u>	<u>9.0</u>	<u>1.25</u>	<u>12.60</u>	<u>7.06</u>	<u>1.28</u>	<u>10.54</u>

Analysis of Faecal Solids (per cent.).

Total mineral matter	25.16	26.86	24.84
CaO	10.05	12.0	12.50
MgO	1.15	1.33	1.62
P ₂ O ₅	7.93	8.48	7.68
Neutral fat	5.53	3.78	8.09
Free fatty acids	14.52	7.12	7.26
Combined fatty acids	19.40	29.45	31.3
Total fats	<u>39.45</u>	<u>40.35</u>	<u>46.65</u>
Percentage of CaO as soaps of total CaO	19.6	25.0	25.5
Urinary phosphorus	1	1.0	1.5
Faecal phosphorus	<u>1.2</u>	<u>1</u>	<u>1</u>
Faecal weight	88.6 grm.	74.0 grm.	54.0 grm.

Case VI. Period I. (Healing rickets.) The retentions of lime, magnesia, and phosphoric acid were but little below the normal level, but no signs of healing were evident on X-ray examination. At the end of the first period, however, healing changes were observed in the radiograms.

The case had been selected to ascertain the effects of human milk fat on the retention of the mineral elements in rickets. The selection was unfortunate. The data suggested that the mode of excretion was still of the rachitic type. The urinary phosphorus was much less than the faecal phosphorus, and the concentra-

Case VI. J. K. Aged 2 years.

Period I. (Healing Rickets.)				Period II. (Human Milk Fat.)				Period III. (Healing Rickets.)				Period IV. (Cod-liver Oil.)			
				<i>Retention of Mineral Elements (gm.).</i>											
	CaO.	MgO.	P ₂ O ₅ .	CaO.	MgO.	P ₂ O ₅ .		CaO.	MgO.	P ₂ O ₅ .		CaO.	MgO.	P ₂ O ₅ .	
Intake	17.29	2.1	22.35	17.50	2.1	23.59		17.50	2.1	23.59		17.50	2.1	23.59	
Output	13.31	1.62	15.42	11.56	1.64	15.87		9.30	1.29	13.49		5.57	1.38	10.38	
	3.98	0.48	6.93	5.94	0.46	7.72		8.2	0.81	10.10		11.93	0.72	13.21	
Retention per kilo per day	0.07	0.008	0.12	0.10	0.008	0.13		0.14	0.014	0.17		0.21	0.01	0.23	
<i>Distribution of CaO, MgO, P₂O₅ in Excreta (7 days).</i>															
Urine	CaO.	MgO.	P ₂ O ₅ .	CaO.	MgO.	P ₂ O ₅ .		CaO.	MgO.	P ₂ O ₅ .		CaO.	MgO.	P ₂ O ₅ .	
Faeces	0.14	0.25	4.22	6.10	0.30	6.26		0.08	0.47	7.77		0.33	0.50	6.72	
	13.17	1.37	11.20	11.46	1.34	9.61		9.22	0.82	5.72		5.24	0.88	3.66	
Total	13.31	1.62	15.42	11.56	1.64	15.87		9.30	1.29	13.49		5.57	1.38	10.38	
<i>Analysis of Faecal Solids (per cent.).</i>															
Total mineral matter	33.66	...	26.52		25.54		16.54	
CaO	15.5	...	9.8		11.35		5.40	
MgO	1.62	...	1.15		1.02		0.91	
P ₂ O ₅	13.18	...	8.22		7.04		3.77	
Neutral fat	4.79	...	6.92		5.73		19.47	
Free fatty acids	7.26	...	11.78		4.52		14.38	
Combined fatty acids	18.15	...	14.50		21.00		11.85	
Total fat	30.20	...	33.20		31.25		45.70	
Percentage of CaO as soaps of total CaO	11.9	...	15.1		18.9		22.3	
Urinary phosphorus	1	...	1		1.3		1.8	
Faecal phosphorus	2.6	...	1.5		1		1	
Faecal weight	85 gm.	...	117.1 gm.		81.3 gm.		97.2 gm.	

tion of mineral matter in the faecal solids (33.66 per cent.) was distinctly above the average level. The study was therefore proceeded with as in Case III, to determine what changes might be effected in the mode of excretion by the addition of human milk fat to the diet.

Period II. (Human milk fat.) A slight increase in the retentions of lime and phosphoric acid took place, that of magnesia being unchanged. The high concentration of mineral matter in the faecal solids was reduced appreciably, but a considerable rise in the faecal weight had also occurred. More phosphorus was eliminated by the urine and less by the faeces. The fatty derivatives underwent no significant change. The effects on excretion during this period recall those of butter fat.

Period III. In order to determine whether the increased retentions were due directly to the human milk fat, a balance experiment was conducted after an interval of a fortnight and the features of excretion again ascertained. The retentions were definitely above the normal. The urinary phosphorus was greater than the faecal phosphorus. No change took place in the percentage values of mineral matter and fatty derivatives, the increased utilization of the mineral elements being related to a fall in the faecal weight.

The data show plainly that healing was continuous from the previous period, and could not be directly attributed to the administration of the human milk fat.

Period IV. (Cod-liver oil.) Cod-liver oil was administered during the last period. The retentions of lime and phosphoric acid were still further increased, the magnesia remaining stationary. A considerable part of the oil was undigested, as shown by the high percentage of neutral fat in the faecal solids, and the escape of an excess of fatty derivatives in the stools led to a rise in the faecal weight. The concentration of mineral matter in the faecal solids was therefore much reduced by fat 'dilution'. The changes in the mode of excretion were the same as in the previous cases. The output of the mineral constituents by the faeces was much diminished, the fall of phosphoric acid being greater than that of the lime in correlation with an increase in the urinary phosphorus. The urinary calcium was definitely increased. Little change was effected in the distribution of magnesia, the high retention being unaltered. Soap formation was still further increased at the expense of the phosphate.

The data of these four periods afford an excellent illustration of the changes which occur in the mode of excretion of the mineral elements as healing progresses.

Case VII. (Active rickets.) The child came under observation while suffering from catarrhal jaundice. An opportunity was therefore presented of determining the retentions of the mineral elements in a rachitic subject when a large excess of free fatty acids persisted in the intestine.

Period I. (Catarrhal jaundice.) During the first period the data showed the characteristic features of excretion associated with a persistent excess of fatty derivatives in the intestine and described in detail in the previous communication (Part IV).

The urinary phosphorus was much greater than the faecal phosphorus, indicating an excessive absorption of this element. The urinary output of calcium was, however, insignificant. A large excess of fatty derivatives had escaped by the bowel, and relatively to the high content of fat (65.61 per cent.) in the faecal solids the mineral concentration (21.3 per cent.) was considerable. The high percentage value of combined fatty acids (47.9 per cent.) showed that excessive calcium soap formation in the intestine had occurred. One-half of the total lime excreted was calculated to exist in this form (50.1 per cent.). In spite of the great absorption of phosphorus the retentions of lime, magnesia, and phosphoric acid were extremely low, the high faecal weight (103.8 grm.) being related to an immoderate output of mineral matter by the bowel.

The data show that the absorption of an excess of phosphorus alone is not

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necessarily followed by an increased fixation of this element. As most of the phosphorus retained is required for bone growth, it is clear that its fixation is dependent on an equivalent utilization of calcium, the lime-phosphoric acid ratio of bone ash being approximately 1.35 : 1. The absorption of an excess of phosphorus might therefore be expected to result in a large urinary output of this element in default of calcium from defective absorption.

Case VII. W. H. Aged $1\frac{1}{2}$ years.

	Period I. (Jaundice.)			Period II. (Post-jaundice.)			Period III. (Cod-liver Oil.)		
	<i>Retention of Mineral Elements (grm.).</i>								
	CaO.	MgO.	P ₂ O ₅ .	CaO.	MgO.	P ₂ O ₅ .	CaO.	MgO.	P ₂ O ₅ .
Intake	11.55	1.61	15.89	11.55	1.61	15.89	11.76	1.61	16.52
Output	10.22	1.42	14.89	10.38	1.37	13.89	8.58	1.12	14.14
	<u>1.33</u>	<u>0.19</u>	<u>1.0</u>	<u>1.17</u>	<u>0.24</u>	<u>2.0</u>	<u>3.18</u>	<u>0.49</u>	<u>2.38</u>
Retention per kilo per day	0.02	0.003	0.015	0.018	0.003	0.029	0.047	0.006	0.035

<i>Distribution of CaO, MgO, P₂O₅ in Excreta (7 days).</i>									
	CaO.	MgO.	P ₂ O ₅ .	CaO.	MgO.	P ₂ O ₅ .	CaO.	MgO.	P ₂ O ₅ .
Urine	0.10	0.37	8.96	0.10	0.26	6.72	0.10	0.15	7.67
Faeces	10.12	1.05	5.93	10.28	1.11	7.17	8.48	0.97	6.47
Total	<u>10.22</u>	<u>1.42</u>	<u>14.89</u>	<u>10.38</u>	<u>1.37</u>	<u>13.89</u>	<u>8.58</u>	<u>1.12</u>	<u>14.14</u>

<i>Analysis of Faecal Solids (per cent.).</i>									
Total mineral matter	21.3	29.4	13.01
CaO	9.75	13.9	5.03
MgO	1.05	1.51	0.58
P ₂ O ₅	5.72	9.69	3.84
Neutral fat	5.05	3.82	24.85
Free fatty acids	12.66	7.53	34.03
Combined fatty acids	47.9	38.00	18.18
Total fat	<u>65.61</u>	<u>49.35</u>	<u>77.06</u>
Percentage of CaO as soaps of total CaO	50.1	27.8	36.8
Urinary phosphorus	1.5	1	1.2
Faecal phosphorus	<u>1</u>	<u>1.1</u>	<u>1</u>
Faecal weight	103.8 gram.	74.0 gram.	168.6 gram.

Period II. (Post-jaundice.) In Period II the jaundice had passed off. The excessive loss of fat had diminished appreciably, though the percentage of fatty derivatives in the faecal solids (49.35 per cent.) was still high. The urinary phosphorus had fallen below the faecal phosphorus. The concentration of mineral matter in the faecal solids had increased, while the faecal weight was reduced. The fall in the percentage value of combined fatty acids was correlated with the increased output of phosphorus in the faeces, the lime as phosphate exceeding the amount existing as soaps. The latter had fallen to 27.8 per cent. of the total lime excreted in the faeces.

These alterations in the distribution of the mineral elements in recovery from jaundice are the same as those described in the previous article (Part IV).

The low retentions of lime, magnesia, and phosphoric acid remained practically unchanged.

Period III. (Cod-liver oil.) In the last period, cod-liver oil was administered, although normal fat absorption, as shown by the data of the previous period, had not been established. The oil was incompletely absorbed and only partially digested; and the escape of a large excess of neutral fat as well as free fatty acids in the stools gave rise to a very high faecal weight (168.6 grm.). The effects associated with a persistent excess of free fatty acids in the intestine were again evident. The urinary phosphorus exceeded the faecal phosphorus. Extreme reduction in the mineral concentration of the faecal solids occurred, and calcium soap formation was increased.

Notwithstanding the defective absorption of fat, the administration of cod-liver oil was followed by a definite rise in the retention of all three elements.

Case VIII. W. K. Aged $\frac{1}{2}$ year. (Healing rickets.)

	Period I.			Period II.			Period III.		
	<i>Retention of Mineral Elements (grm.).</i>								
	CaO.	MgO.	P ₂ O ₅ .	CaO.	MgO.	P ₂ O ₅ .	CaO.	MgO.	P ₂ O ₅ .
Intake	10.11	1.30	13.16	10.11	1.3	13.16	11.80	1.64	15.71
Output	6.74	0.80	8.01	3.97	0.71	6.10	3.45	0.86	6.53
	<u>3.37</u>	<u>0.50</u>	<u>5.15</u>	<u>6.14</u>	<u>0.59</u>	<u>7.06</u>	<u>8.35</u>	<u>0.78</u>	<u>9.18</u>
Retention per kilo per day	0.10	0.015	0.15	0.18	0.017	0.21	0.23	0.02	0.26
	<i>Distribution of CaO, MgO, P₂O₅ in Excreta (7 days).</i>								
	CaO.	MgO.	P ₂ O ₅ .	CaO.	MgO.	P ₂ O ₅ .	CaO.	MgO.	P ₂ O ₅ .
Urine	0.10	0.098	2.24	0.10	0.175	4.45	0.21	0.28	5.25
Faeces	6.64	0.71	5.77	3.87	0.54	1.65	3.24	0.58	1.28
Total	<u>6.74</u>	<u>0.81</u>	<u>8.01</u>	<u>3.97</u>	<u>0.715</u>	<u>6.10</u>	<u>3.45</u>	<u>0.86</u>	<u>6.53</u>
	<i>Analysis of Faecal Solids (per cent.).</i>								
Total mineral matter	31.9	18.9	17.6
CaO	15.1	5.65	9.0
MgO	1.62	0.72	1.63
P ₂ O ₅	13.12	2.4	3.58
Neutral fat	4.77	7.10	4.54
Free fatty acids	11.23	16.70	4.11
Combined fatty acids	24.0	23.80	38.10
Total fat	<u>40.0</u>	<u>47.60</u>	<u>46.75</u>
Percentage of CaO as soaps of total CaO	16.2	42.9	43.2
Urinary phosphorus	1	2.7	4.1
Faecal phosphorus	<u>2.5</u>	<u>1</u>	<u>1</u>
Faecal weight	44 grm.	68.6 grm.	36 grm.

Case VIII. Period I. (Healing rickets.) The history of this case is similar to that of Case III. The clinical features and the X-ray examinations of the bones appeared to indicate that the disease was active. The somewhat high percentage values of the mineral constituents of the faecal solids together with the low urinary phosphorus also suggested that excretion was of the rachitic type. The retentions of lime, magnesia, and phosphoric acid were normal, however. Doubt was therefore entertained as before as to the phase of the illness.

The child was obviously unsuitable as a subject for testing the effects of any therapeutic agent on low retentions of the mineral elements, and was maintained on the measured intake of milk for a period of observation.

Periods II and III. A balance experiment was commenced a week later, but was spoiled by the onset of vomiting. X-ray examination showed no changes in ossification.

Three weeks later a successful balance experiment was carried out. The retentions of lime, magnesia, and phosphoric acid had now attained very high values. The urinary phosphorus was considerably in excess of the faecal phosphorus. The concentration of mineral matter in the faecal solids was greatly reduced, due allowance being made for the increase in total fatty derivatives. The diminished percentage of phosphoric acid in the faecal solids relatively to the lime, and the rise in the output of urinary phosphorus at the expense of the faecal phosphorus, indicated that an excessive absorption of this element had occurred. A greatly increased proportion of the calcium was eliminated as soaps, while the excretion as phosphate was reduced.

These changes, which are identical in nature with the modifications in mineral excretion following the administration of cod-liver oil observed in the preceding cases, together with the abnormally high retentions, confirmed the suspicion that healing was in progress. At the end of the second period X-ray examination showed no changes at the epiphyses of the wrist-joints, and another fortnight elapsed (Period III) before definite signs of increased calcification were discernible on the X-ray plates.

There is little room for doubt that calcification had been progressively increasing for several weeks prior to the date of this X-ray examination.

Case IX. M. McG. Aged 7 years. (Healing rickets.)

Retention of Mineral Elements (grm.).

	CaO.	MgO.	P ₂ O ₅ .
Intake	24.22	3.36	32.34
Output	6.01	1.40	15.86
	<u>18.21</u>	<u>1.96</u>	<u>16.48</u>
Retention per kilo per day	0.11	0.01	0.10

Distribution of CaO, MgO, P₂O₅ in Excreta (7 days).

	CaO.	MgO.	P ₂ O ₅ .
Urine	0.34	0.69	11.78
Faeces	5.67	0.71	4.08
Total	<u>6.01</u>	<u>1.40</u>	<u>15.86</u>

Analysis of Faecal Solids (per cent.).

Total mineral matter	23.32
CaO	11.35
MgO	1.42
P ₂ O ₅	8.16
Neutral fat	9.81
Free fatty acids	5.89
Combined fatty acids	20.5
Total fat	<u>36.20</u>
Percentage of CaO as soaps of total CaO	18.4
Urinary phosphorus	2.9
Faecal phosphorus	<u>1</u>
Faecal weight	75 grm.

Case IX. (Healing rickets.) This study of rickets in an older subject is included in the present series for comparative purposes. X-ray examination showed that the disease had passed spontaneously into the healing stage. The retentions of lime, magnesia, and phosphoric acid were normal, and the mode of excretion was in marked contrast to that in the active stage of the disease.

An appreciable amount of calcium was found in the urine. The urinary magnesia formed one-half of the total excreted. The urinary phosphorus was nearly three times as much as the faecal output. The concentrations of mineral matter and total fatty derivatives were within normal limits. Of the latter, the greater part consisted of combined fatty acids.

Discussion.

The active stage. The data recorded in Period I of the series plainly show that the diminished retentions of the mineral elements in active rickets are associated with an excessive loss of mineral salts in the faeces. The urinary calcium is almost negligible; the urinary magnesia forms only a small proportion of the total amount excreted; and the excretion of phosphorus by the kidney is much reduced in comparison with the high faecal output.

The undue loss of mineral matter by the bowel is expressed in two ways. More commonly, the percentage of total fatty derivatives in the faecal solids lies within normal limits, and the concentration of mineral matter is above the average level. High percentage values of lime, magnesia, and phosphoric acid are then found. In exceptional cases the concentration of each of the individual mineral constituents is approximately normal as a result of fat 'dilution' from the escape of an excess of fatty derivatives, and the loss of the mineral elements is related to a high faecal weight.

The composition of the faecal solids and the distribution of the mineral elements in the urine and faeces indicate clearly that the greater part of the mineral matter eliminated by the bowel consists of lime existing as phosphate. In the cases uncomplicated by the excretion of an excess of fatty derivatives, the urinary phosphorus is uniformly low in comparison with the faecal phosphorus; the maximum amount of lime which could possibly exist as soaps, calculated from the combined fatty acids, is a very small proportion of the total lime escaping in the faeces; and finally, high percentage values of lime are associated with correspondingly high values of phosphoric acid. In the excessive loss of mineral matter from the bowel, both of the essential bone-forming elements are involved, the calcium restricting the phosphorus to the intestine in an insoluble form. The data of excretion in the active stage of the disease are therefore entirely in harmony with the view expressed, that the diminished retentions of the mineral elements are dependent on their defective absorption from the intestine.

The healing stage. The mode of excretion when healing occurs is widely different from that observed during the active stage of the illness. The excess of mineral matter disappears from the faeces as the retentions of lime, magnesia, and phosphoric acid increase, and this is expressed by a fall in the percentage

values of the mineral constituents of the faecal solids or by a reduction in the faecal weight. The urinary excretion of phosphorus increases, and the faecal output lessens. The ratio of urinary to faecal phosphorus represented by a fractional number, $\frac{1}{2}$ or $\frac{1}{3}$, in the active stage of the illness may attain values such as $\frac{2}{1}$ or $\frac{3}{1}$ as healing advances. The urinary calcium and magnesia tend to increase. On account of the very high output of phosphorus by the urine, the fall in the percentage value of phosphoric acid in the faecal solids is greater than that of the lime, and a larger proportion of the total lime in the faeces is found existing as soaps.

These changes in the mode of excretion clearly show that the rise in the retentions of the mineral elements is accompanied by an increased absorption from the intestine. The absorption of an excess of phosphorus, which is indicated by the high ratio of urinary to faecal phosphorus, is an outstanding feature of the healing process, and affords a feasible explanation of the increase in the concentration of inorganic phosphate of the blood, which occurs not only after the administration of cod-liver oil in rickets, but also on exposure of the rachitic subject to ultra-violet radiations (3). The alteration in the ratio of urinary to faecal phosphorus appears to constitute a valuable diagnostic sign of healing. It was originally observed fifteen years ago by Schabad (4), who, however, possibly misinterpreted its significance. Schabad obtained negative retentions in some of his balance experiments, and naturally concluded that the high faecal phosphorus characteristic of the active stage of the disease was due to phosphorus excretion *into* the gut following decalcification of the bones and loss of phosphorus from the soft tissues. The duration of his balance experiments was very short and possibly insufficient to permit of a great degree of accuracy in the determination of retention values. In the metabolic studies made by the writer, negative retentions have never been found in infantile rickets, and the theory of excessive decalcification has been regarded as inadmissible. Nevertheless, Schabad's observations on the features of excretion which distinguish the active from the healing stage of the disease are fully confirmed by the data of the present series.

The increased fixation of the bone-forming elements, which follows the increased absorption of mineral matter, is shown by the rise in the retention values. As found in the earlier work an excess of phosphorus is retained over the equivalent amount of calcium required in bone growth (Part II). The relatively small retention of magnesia, roughly about one-tenth that of the lime, is probably correlated with its slight utilization in skeletal development and its meagre provision in milks. The magnesia content of cow's milk is about one-eighth that of the lime.

The histories of the two cases in which spontaneous healing occurred (Cases III and VII) serve to emphasize the importance of biochemical data in the diagnosis of the phase of the illness. The alterations in the mode of excretion which are associated with the healing process, and dependent on the increased utilization of the mineral elements, can be readily detected by quantitative methods long before healing effects are apparent clinically. The value of such

methods as a means of following accurately the course of the disease has also been referred to in the previous article (Part IV), in which the changes in excretion incident to recovery from jaundice are described.

It may be of interest to recall that in the contribution on the metabolism of calcium and phosphorus in infantile rickets already cited, two cases were recorded in each of which commencing pathological changes in the bones could not be detected by X-ray examination, while a diagnosis of rickets was indicated by the low retentions of lime and phosphoric acid estimated from balance experiments. Later examination showed that both subjects were suffering from the disease. A similar case was also recorded by Findlay, Noël Paton, and Sharpe (5).

When the comparatively low rate of calcium utilization in the human subject is remembered (about 0.8–1.0 grm. CaO per day in infants), it is clear that an appreciable interval of time, measurable at least in weeks, must elapse before commencing rarefaction in a growing bone or increasing deposition of lime salts in a 'softened' bone will become evident clinically. In the diagnosis of the phase of the illness, X-ray examination may easily be fallacious. This consideration is perhaps of most importance in the investigation of therapeutic effects. A subject may be selected for observation when the active stage of the illness is passing. X-ray examination of the bones will then show the rachitic features at their worst, and will fail to disclose that healing is perhaps in progress. The healing changes revealed by later examination might therefore be attributed quite erroneously to some therapeutic measure adopted during this period. Spontaneous healing is the natural termination of the disease. The rapidity with which this process may supervene on the active stage has perhaps been lost sight of by some investigators.

The influence of fats in the diet. The effects produced by the addition of the fats to the milk are in accordance with the results of experimental work on animals. It has been shown by numerous observers that the fish-liver oils prevent the onset of rachitic changes in the bones of young animals, but not the animal fats or vegetable oils.

No increase in the retention values followed the administration of olive oil and butter fat, while an increase was at once evident when cod-liver oil was substituted for these.

The changes in the mode of excretion which result from the use of cod-liver oil are clearly due to increased absorption of the mineral elements and to the presence of an excess of fatty acids in the intestine. The latter condition is apparently induced with ease by the administration of the oil, for the characteristic features of excretion, with which an excess of fatty acids in the intestine is associated, are evident more or less in all the cases recorded. The greater absorption of the mineral elements, however, is not necessarily due to a rise in the concentration of fatty acids in the gut, though the *excessive* absorption of phosphorus is related to the increased linkage of calcium with fatty acids in the intestine, as shown by the rise in combined fatty acids of the faecal solids after

administration of the oil. In minor degree this also occurred on the addition of butter fat to the milk.

Zucker, Johnson, and Barnett (6) found that the fatty acids of cod-liver oil when fed to rachitic rats had no curative action. The writer, in collaboration with Mr. A. Watson, recently confirmed their results by feeding experiments on puppies. Out of a litter of five animals, three had olive oil and two the isolated insoluble fatty acids of cod-liver oil added to a basal diet from the time of weaning. Rachitic changes developed in the bones of all the animals, though more slowly and to a lesser degree in the latter group. An interesting feature of this experiment was the rapid healing which occurred without change of diet or environment in both groups.

The alteration in the gastro-intestinal functions which permits the increased absorption of the mineral elements may possibly be a rise in the hydrogen-ion concentration of the intestinal contents. The elimination of an excess of calcium by the bowel as insoluble phosphate of lime in the active stage of the illness, and the low output of phosphorus by the urine, are in marked contrast to the mode of excretion in the healing stage, when an excess of the acid radical is absorbed and excreted by the kidney, and the absorption of lime and magnesia is greatly increased. The differences in the two modes of excretion are roughly parallel with those observed in alkali and acid feeding experiments.

In this connexion the recent work of Abrahamson and Miller (7) is of interest. These workers have found that the pH values of the gastric and intestinal contents of rats on a 'rachitic' diet were much higher than in control animals receiving cod-liver oil. A series of experiments in which animal fats and the vegetable oils are employed would seem to be necessary, to determine whether the fish-liver oils have a specific action in increasing the H-ion concentration of the intestinal contents. The insoluble fatty acids of high molecular weight can have but little effect in this direction, and a much greater proportion of the soluble and more highly dissociated lower fatty acids, such as butyric and caproic, is furnished by butter fat on hydrolysis, than by cod-liver oil. The reaction of the intestinal contents may, however, be subject to considerable variation through alterations in gastric acidity and the amount of alkaline secretion poured into the gut. In relation to the absorption of the mineral elements in the active and healing stages of the disease, this factor would appear to be worthy of further investigation.

Although the mode of action of cod-liver oil is unknown, the data of the present series of studies suggest that its prophylactic and curative properties are dependent on changes induced in the gastro-intestinal tract which permit free absorption of the mineral elements, and that the latter is the essential condition in the prevention and cure of rickets.

Summary.

1. Metabolic studies of nine cases of infantile rickets have been made, in each of which the mode of excretion was determined from the composition of the faecal solids and the distribution of the mineral elements in the urine and faeces.

2. Low retentions of lime, magnesia, and phosphoric acid were found in the active stage of the disease in association with a type of excretion which has the following abnormal characteristics :

- (a) An excess of mineral matter is excreted in the faeces which consists mainly of lime existing as phosphate.
- (b) The percentage of total mineral matter in the faecal solids, and of the lime, magnesia, and phosphoric acid, are increased.
- (c) The concentration of total fatty derivatives lies within normal limits ; but in conformity with the elimination of calcium in the faeces almost wholly as phosphate, the combined fatty acids tend to be relatively low.
- (d) The urinary phosphorus is considerably less than the faecal phosphorus.

3. This mode of excretion is discussed, and is shown to be in accordance with the hypothesis that the faulty utilization of the bone-forming elements in infantile rickets is dependent on their defective absorption, possibly secondary to some alteration of the gastro-intestinal functions.

4. When healing occurs the excess of mineral matter disappears from the faeces and the mode of excretion undergoes extensive changes which possess diagnostic significance.

- (a) The concentration of mineral matter and of the individual mineral constituents of the faecal solids are reduced.
- (b) The reduction in the percentage of phosphoric acid is greater than that of the lime.
- (c) The urinary phosphorus rises, and finally is in excess of the faecal phosphorus.
- (d) The percentage of combined fatty acids increases as the output of phosphorus by the urine becomes excessive.
- (e) The urinary calcium and magnesium may show appreciable increase.

5. The alterations in the mode of excretion as healing progresses are due to increased absorption of the mineral elements from the intestine. The absorption of phosphorus is much in excess of requirements.

6. The effects produced by the addition of cod-liver oil, butter fat, and olive oil to the diet in active rickets are compared.

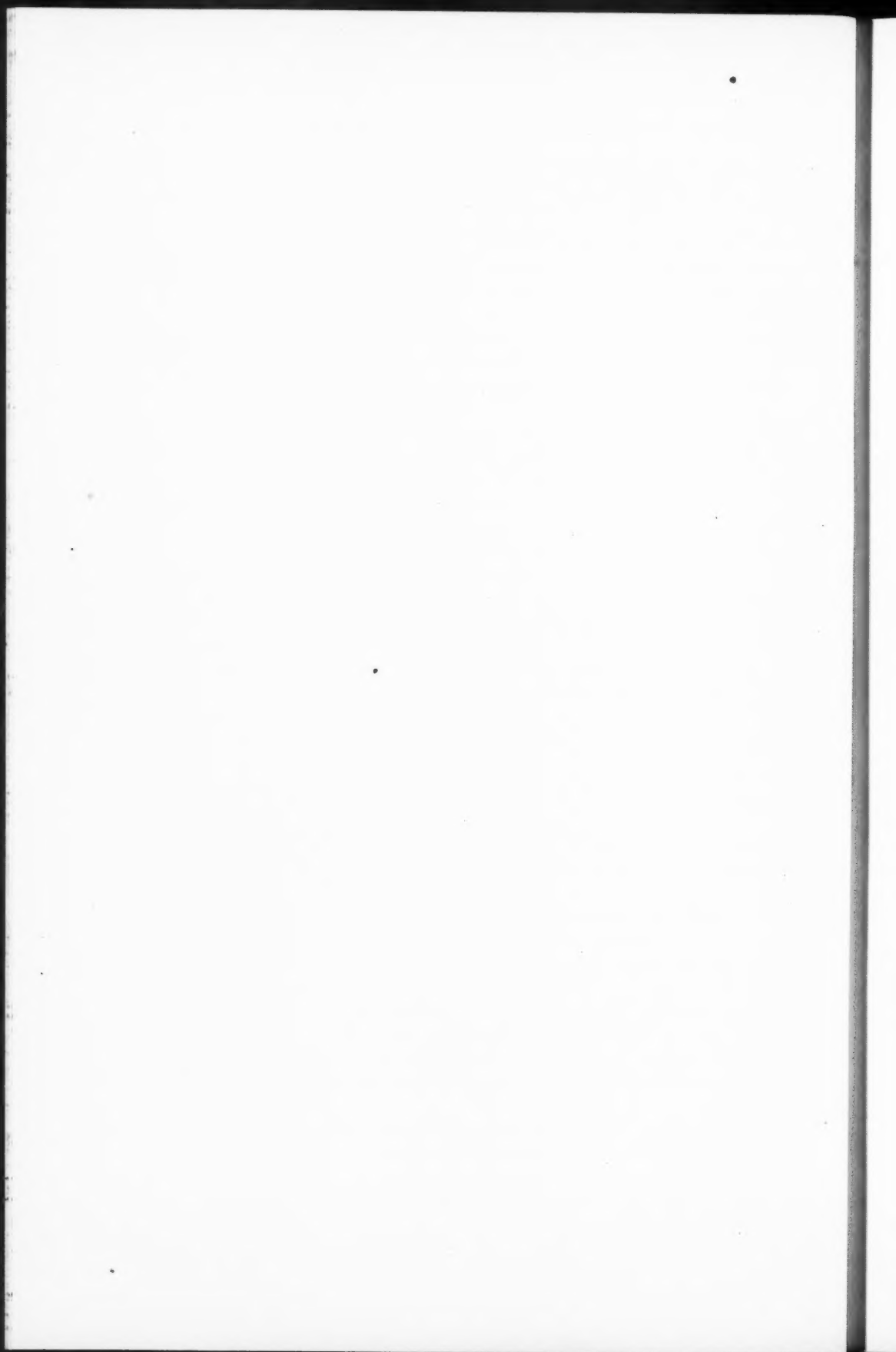
7. Cod-liver oil alone has a specific effect in increasing the retention values of the mineral elements, the healing changes being initiated by an increased absorption of the latter.

8. The mode of action of cod-liver oil is discussed. It is suggested that its prophylactic and curative effects are dependent on altered conditions of the gastro-intestinal tract which permit free absorption of the mineral elements, and that the latter is the essential factor in the prevention and cure of rickets.

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THE EFFECT OF EXERCISE ON THE PULMONARY VENTILATION AND RATE AND DEPTH OF BREATHING IN CHRONIC BRONCHITIS^{1, 2}

PAPER I

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Introductory.

THE effect of residence in an increased percentage of oxygen has been investigated in detail on several occasions during the last three years. The eight patients dealt with in this and the succeeding communications were short of breath on exertion, and in most of them the breathlessness was due to chronic bronchitis. Each time for a week they spent the night and most of the day in a chamber containing about 40 per cent. oxygen, and various observations were made before, during, and after this period. The effect of exercise on the ventilation and respiratory exchange was specially investigated, and the exercise chosen was stepping on and off a wooden block thirteen inches high; a lower block would have been easier and more like the exercise in stair climbing to which every one is accustomed, but many data about the pulse-rate had already been obtained for this exercise, and we wished to obtain comparable results for the ventilation and metabolism (16). As some of the men were not sufficiently fit to mount this step directly, an intermediate step was used by them and by some controls.

The respiratory data were obtained with a closed circuit in which a spirometer was included, and the apparatus and the degree of accuracy reached with it will be described elsewhere. The observations at rest were made with the subject sitting comfortably in a chair before the exercise, and though they always lasted for at least fifteen minutes, there were variations probably from the effect of meals and of previous exertion. These differences were minimized as far as possible, but if observations are to be made at all times of the day they cannot altogether be avoided. When the exercise was finished the subject sat down and

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³ Working under the tenure of a Beit Memorial Research Fellowship.

rested in the same position as before, and observations were continued for at least ten minutes, as with most of these exercises this was sufficient for almost complete return to the resting condition.

Observations were made in March and in June 1923, and in February-April 1924, and these are referred to as the first, second, and third series. At first we had not realized the importance of continuing the exercise long enough for equilibrium to be attained, and the subject only did one minute's exercise of twelve steps. Three patients (B., P., and S.) and four healthy students were examined on twenty-one occasions. Subsequently, whenever possible, the exercise was continued for three minutes, and in health at the rates of exercise used this is long enough to get very near the position of equilibrium.

In the second series we examined four students and three patients (H., W., and B., the last being much better than previously). The rate of exercise was twelve steps a minute, and less frequently eighteen steps a minute, in each case for three minutes, and observations at these rates were made on twenty occasions. During most of the time W. was only well enough to continue the exercise for one minute, so these six observations are described with the earlier ones of the first series.

In the third series four students and three patients (M., C., and G.) were examined. As they were less fit than most of the others, and as before W. had been unable to go on for more than one minute, a slower rate was chosen, six steps a minute for three minutes. The thirteen-inch step was too high for these men and an intermediate step was inserted. Even this rate could not be kept up by G., so he only did four steps a minute for three minutes, and a few observations were made on M. at this rate for comparison.⁴ Thirty-two observations were made at six steps a minute, and sixteen at the slower rate.

A few observations at twelve steps a minute for three minutes made on patients W., S., and P. in 1925 have been included to make our data more complete.

If the difficulty of these exercises is judged by the oxygen consumption which they require, six steps a minute is slightly easier than walking two and a half miles, and twelve steps rather easier than four miles an hour. (Cf. Douglas (2) and the following paper.)

Before discussing the effect of oxygen on these men and on their ability to take exercise, the pulmonary ventilation and respiratory exchange during and after exercise in those who are short of breath and not undergoing oxygen treatment must be described, and compared with the normal. The ventilation and the rate and depth of breathing are dealt with in this paper, and the respiratory exchange under the same conditions is reported in the following paper. In a third paper the oxygen chamber will be described, and the effect of residence therein on the clinical condition of these patients, on their ability to take exercise, and on their ventilation and metabolism during exercise.

⁴ A normal student, Cr., has recently been investigated at this rate.

Clinical Condition of the Patients.

Full clinical notes of the patients investigated will be given when the result of oxygen treatment is described, but a short account will be given here.

S. was of good physique but had signs of chronic bronchitis and emphysema. He complained of severe breathlessness since serving in Gallipoli, but carried out the exercises more easily than the other patients. In 1925 his general condition was perhaps a little worse.

P. had bronchitis and emphysema, and was admitted with an attack of acute bronchitis and heart failure, brought on by hard work in a hot atmosphere, from which he had recovered when these investigations were made. Two years later he was able to do quite hard work.

B. was admitted with acute bronchitis and right-sided failure, but this last had disappeared a month later at the time of our investigations. His acute history extended over the previous six months, but he had had symptoms for fifteen years. During the first series he was very breathless, while during the second he was free from any acute bronchitis and was probably at his best.

W., when first examined, had severe asthma and bronchitis, cyanosis and dyspnoea, and was only able to keep up the exercise for a short time, because of violent coughing. He improved considerably while in hospital and had almost recovered from his acute attack when he did the exercise for three minutes. He had only had these attacks of asthma and acute bronchitis for a year, but from then till November 1925 he had frequent acute attacks and gradually became more crippled. These clinical changes were reflected in changes in his breathing.

C. was of the same build as B., and his bronchitis had been getting worse each winter for ten years. There was a good deal of chronic emphysematous change in his lungs, and when he was first examined there was acute bronchitis with copious sputum. At first his coughing and expectoration often prevented him wearing the mask continuously, but this improved a good deal and he was a good patient, trying to carry out instructions, and willing to put up with a good deal of breathlessness.

In G. his pulmonary condition had come on suddenly eighteen months before, and was of an asthmatic type and very crippling. He was extremely short of breath on exertion and sometimes while at rest, and had little sputum but a very troublesome cough. He was a bad subject for these investigations, as it was often difficult to persuade him to keep the mask on to continue the exercise. He died two years later; but the cause of death is not known.

The other two patients fall into a rather different group. H., an ex-soldier, was diagnosed as a case of effort syndrome. He was obviously breathless, but except for occasional low-pitched rhonchi his lungs generally showed no physical signs of disease. In spite of this the results, as far as respiration was concerned, were very similar to those of the others with bronchitis.

M. was a large muscular man with myocardial degeneration and little involvement of his lungs. In many ways the results obtained with him were very different from the others, but he is discussed here because he was in the oxygen chamber with the others and the conditions of observation were the same as for them, while other cardiac patients investigated by one of us have been dealt with rather differently. He was an excellent subject, ready to do anything, and thought that the exercise did him good. His condition was very little changed two years later.

The Type of Respiration at Rest.

As the normal standard we can take the average results obtained on twelve students at rest, viz. ventilation 7.8 litres, rate of breathing 15, depth 520 c.c. The ventilation was always between 6.5 and 9.0, except in one man weighing 79 kilos, where it was 11.2 litres; the rate varied between 12 and 18, except once when it was 22. The depth was between 370 and 580 c.c., except in the man already mentioned, in whom it was 700 c.c.: in more than three-quarters of the men it was between 440 and 580 c.c. These volumes and all others in this paper are given as they were measured at room temperature (generally 15°–17° C.) saturated with vapour at the prevailing barometric pressure, i. e. about six per cent. higher than they would be, reduced to normal temperature and pressure. They are naturally higher than those found by Debenham and Poulton (6) under basal conditions, and agree with the generally accepted figures (19).

In the breathless patients the pulmonary ventilation was about normal, but the rate was generally increased, sometimes considerably, and the depth reduced. The depth in the patients was only in one case above 520 c.c., the average for the normals, and the average for the patients, 385 c.c., was almost as small as any value found in health.

Except for H. and M., who had no appreciable disease of the lungs, G. was the only patient with a respiration rate consistently as low as 20, and W. with acute bronchitis and probably little chronic change in the lungs was the only bronchitic in whom the depth was as much as 425 c.c.

In S. the rate was over 30, and in B., W., and C. about 25, and in S., B. (first series), C., and G. the depth was less than 400, and in P. less than 300 c.c. These figures are enough to show that in chronic bronchitis at rest the breathing is generally rapid and shallow. Complete figures are given in Table I at the end.

This rapid shallow breathing has long been recognized as one factor in the production of breathlessness, and its occurrence in various cases was emphasized by Beddard and Pembrey in 1908 (1). More recently its importance in dyspnoea has been discussed by Peabody (5), and in many types of anoxaemia, and especially in cases of disordered action of the heart with nervous symptoms, it has been described and investigated by Haldane, Meakins, and Priestley (8, 10, 11, 14). Its significance will be discussed later. Table I also shows that there is considerable variation from day to day in the breathless, more than in most healthy, subjects. As the clinical condition and the ability to take exercise improved there was a return (partial or complete according to the amount of recovery) to the normal standard.

The Type of Respiration during and after Exercise.

In health the increase in ventilation which is required during slight exercise is obtained mainly by increasing the depth of breathing without much increase of rate (see Table II, where a rate of exercise which increased the metabolism

nearly 200 per cent., only raised the rate of breathing from 16 to 18). Later, when the exercise is considerably increased, the breathing is also much faster. This is well shown in some figures published by Douglas (2); when walking at two miles an hour the rate of breathing was 14.7 and the depth 1,270 c.c., but when the pace was increased to five miles an hour the rate was only raised to 19.5 and the depth to 3,145 c.c. In similar experiments by Campbell, Douglas, and Hobson (12) the pulmonary ventilation was often increased up to 60 litres before the respiration rate rose to 30 a minute.

The findings in our normals at the various rates of exercise agree with these conclusions and show the same general features as those published by Krogh and Lindhard (3, 7), Hill, Long, and Lupton (23), and others (12, 21).

Our patients who were short of breath have been investigated in exactly the same way as our normals, because there must be a small instrumental lag in the apparatus, and any error due to this will be the same for both groups.

First series.—The exercise was twelve steps a minute for one minute. Twenty-one observations were made on four subjects, and in each case the same type of result was obtained. The ventilation was increased about as much as in health, though the increase was less, relatively to the resting value. The results of the second and third series show that the ventilation in the first minute is not a good guide to the more important changes which take place when the exercise is continued for longer.

The rate of breathing was much faster in the breathless than in the healthy, so that the shallow breathing was even more noticeable during exercise than at rest (see Tables III and IV). The contrast is well shown by the following figures: The average rate at rest in health was 14, and was increased to 19 during work; in those short of breath the average varied from 19 to over 30 at rest, and from 25 to 38 during this exercise. It was the same with the depth of breathing. During exercise in the healthy men it was generally nearly double the rest value (about 1,000 c.c.) and never less than 750, while in the bronchitics it was never above 670, and was generally between 500 and 600 c.c.

At first W. was very breathless and cyanosed and often had Cheyne-Stokes breathing when wearing the mask, but later, when he was able to do the exercise for three minutes, he was much better. On one occasion, which may be taken as typical, he showed slight periodicity in his breathing at rest and an increase of this during exercise with practically no increase in the ventilation. One and a half minutes after the exercise his breathing became absolutely regular, perhaps under the influence of the carbon dioxide which had been retained, but later again a real Cheyne-Stokes breathing developed. Many breaths during exercise were only 200 c.c., and just after, when they were deepest, they varied from 350 to 580 c.c. Ten minutes after, when there was definite periodicity, three consecutive periods of twenty seconds gave 12 breaths of average depth 220 c.c., 10 of 270, and 8 of 380 c.c.

The difference between healthy men and men short of breath was even more striking after the exercise. In the healthy there was a rapid drop in the ventila-

tion, so that by the second minute it was nearly back to normal after very light exercise, while in the breathless the drop was much more gradual. This is well shown in the first of the charts, in all of which the ventilation at rest is shown as 100, and during and after exercise as a percentage increase above this; this has the advantage of making clearer the relative rates of return. We have averaged all the observations on any one individual, as the figures to be dealt with otherwise would be so numerous, and have satisfied ourselves that this procedure has not introduced any error into our conclusions. In two of the men, B. and P., the ventilation in the first minute after stopping was higher than during the exercise, and the fall did not start till the second minute.

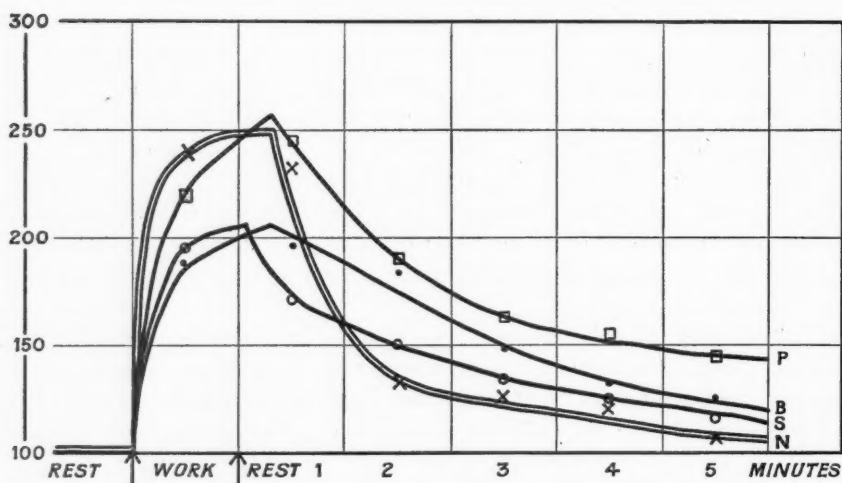


CHART I. Pulmonary ventilation during one minute's exercise of 12 steps a minute and for five minutes after, expressed as a percentage of the ventilation at rest, which is taken as 100. The double line denotes the average result in four healthy students, and the single lines the average of all observations on three subjects with chronic bronchitis (P., B., and S., first series.)

Second series.—The exercise was 12 steps a minute for three minutes, and in a smaller number of cases 18 steps a minute for three minutes (see Chart II and Tables V and VI). The respiration during the one minute's work of the first series and during the first minute at 12 steps of the second series may be compared (Tables IV and V). In B. the ventilation was much the same on each occasion, but this alone gave a false impression of the breathlessness, as in the bronchitics but not in the normals it continued to increase considerably during the second and third minutes of work. In W. the ventilation for the first minute was less in the second series, but his clinical condition was greatly improved. In 1925, when his permanent condition had become worse, the result was very similar to that obtained when he could only do 12 steps for one minute. In S. the result in 1925 was higher, but this was when his general condition was perhaps a little worse. In P. also the ventilation was a little higher in 1925, but the resting

value was also considerably higher than in 1923. Comparing Charts I and II suggests that different normal standards were being used, and unfortunately three of the four men during the exercise for one minute had not previously used the apparatus and rather over-ventilated. The fourth gave almost the same result in both series. Incidentally the normal men who did 12 steps for three minutes were above the average as regards fitness, and those who set the standard for the first and third series were probably a little below the average.

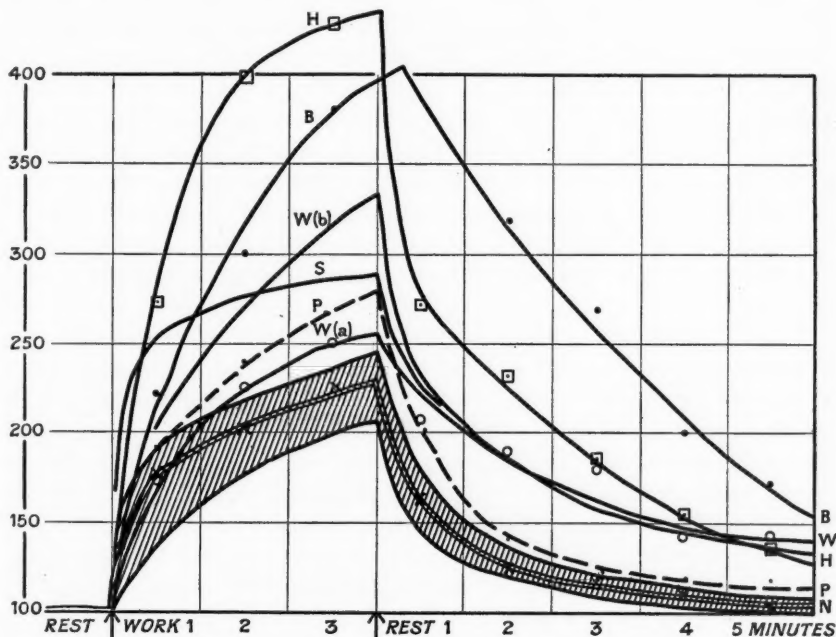


CHART II. Pulmonary ventilation during three minutes' exercise of 12 steps a minute and for five minutes after, expressed as a percentage of the ventilation at rest, which is taken as 100. The double line denotes the average result in four healthy students, and the range of variation is represented by the shaded area. The single lines give the average of all observations on B. with chronic bronchitis, H. with effort syndrome, and a single observation on W. (second series). Single observations on W., S., and P. made in 1925 are also included (W. (a) refers to 1923, W. (b) to 1925). P. in 1925 stated that he was hardly short of breath and had been at work for more than a year. Note the improvement in his case from the result obtained in Chart I in 1923.

What is more important is that the normals throughout the three minutes showed only a small increase in ventilation and depth, so that even in the first minute ventilation appeared almost adequate. On the other hand, B.'s ventilation during the third minute of work was enormously greater than the normal. His rate of breathing throughout the three minutes was about the same as before (i.e. much above the normal figures), and the depth in the third minute of work was much increased and was now up to the normal figure. The result was very similar with H., although his breathlessness was due to 'effort syndrome'. The shallow respiration means that the true alveolar ventilation was much less than

the pulmonary ventilation, but even allowing for this the alveolar ventilation of most of these patients was much above normal during and after the exercise. In the case of W. the ventilation was not increased, though the breathing was shallow and the rate of respiration was high. He had greatly improved by this time.

In 1925 W. (Table V) showed a similar response to H. and B., though the ventilation was not quite so much increased. So did S., who previously had only been tested with one minute's work; actually his ventilation was greater than any of the other bronchitics, but the percentage increase was not so much, because of his high ventilation at rest both in 1923 and again in 1925. The result on P. in 1925 is very interesting, for after three minutes' exercise it was only just outside the normal range. He said that he was hardly short of breath and was then able to do quite hard work. Unluckily he was not tested at 12 steps a minute for three minutes in 1923, but when he did the same exercise for one minute only in 1923 his ventilation was almost as great as, or relatively to the resting value, much greater than when he did it for three minutes in 1925.

In general the ventilation was about half as much again as in the normals, and the rate was generally over 30, and sometimes over 40, instead of 20 or less as in the normals.

In this series, just as when the stepping was for only one minute, there was in the pathological subjects a much slower drop and a much less complete return to the resting condition after the exercise. In this period, too, the rate of breathing was greater in the bronchitic than in the healthy subjects. In fact these subjects were still breathing more rapidly five minutes after the exercise than did the normals during it. The depth of breathing was also less among the bronchitics, but this was not such a striking feature.

The observations at 18 steps a minute (Table VI) need not be considered in detail. They illustrate the same general principles as the lighter exercises. The rate of breathing in these patients cannot apparently be increased further; but the depth is now increased practically up to the normal value, so that there is still a much higher ventilation than in health.

Third series.—The exercise was 6 steps a minute for three minutes (see Table VII). The subjects were very unfit, C. having chronic bronchitis of many years' standing, with profuse expectoration, G. having perhaps even greater incapacity, due to pulmonary disease of asthmatic type of about eighteen months' duration, and M. having myocardial degeneration. A word must be said about the four normals, all medical students, in this last series. The range was wide, and so all the results have been given in detail. Ch. was athletic and fit at the time of the experiment. The other three did not take regular exercise, and Le. complained of feeling below par, but was doing his ordinary hospital work. His breathing was rather shallow, but the ventilation and rate rapidly fell to normal at the end of the exercise. Unfortunately, G. was unable to reach the stage of exercise chosen and only did 4 steps a minute for three minutes, but some observations were made on M. at this rate for comparison and we have also one normal, Cr. In C. the increase in ventilation during work was less than normal,

in contrast to the results of the second series. This was because the breathing tended to remain shallow.

M., in whom the etiology of the breathlessness was quite different, showed quite a different result. He was able to increase his depth of breathing to the normal extent, and therefore increased his ventilation rather more than the normal. Comparison of G., M., and the normal Cr. at 4 steps a minute shows that, like C., G.'s ventilation during work was subnormal and the breathing shallow. The results are shown in Chart III and in Table VII. The three patients are very different, but they mostly show the slower fall in ventilation and rate of breathing after work, and the less complete return to the resting condition. One of the interesting points was the constancy of the results for each of the three, so that with the set of figures or the record on the drum (see Chart IV) for any one observation it was easy to see from which of the three

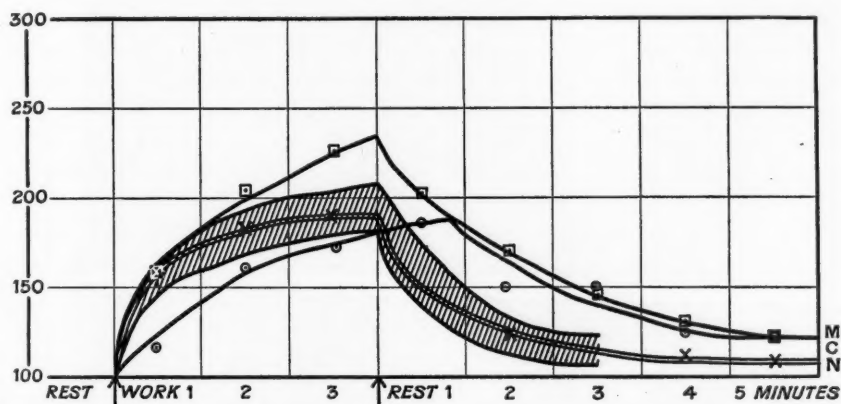


CHART III. Pulmonary ventilation during three minutes' exercise of 6 steps a minute and for five minutes after, expressed as a percentage of the ventilation at rest, which is taken as 100. The double line denotes the average result in four healthy students, and the approximate range of variation is also given. The single line gives the average of all observations on one patient with chronic bronchitis (C.) and one with myocardial disease (M.).

subjects they had been obtained. Thus M. had a high ventilation at rest and could increase it by 140 per cent. during work, but was not back to normal in ten minutes; at the lowest rate of exercise the increase was 100 per cent. C. had a moderate ventilation at rest, and was more nearly back to normal in ten minutes. G. had the lowest ventilation at rest, only increased it by 50 per cent. during work, and was quite back to normal in ten minutes. Thus his increase was much less than M. and Cr. at the same rate of work.

One of the most striking points in common between all the subjects with pulmonary disease so far examined was the rapid shallow breathing at rest and during and after exercise. With M., whose trouble was myocardial with practically no involvement of the lungs, the results were absolutely different. The depth of breathing at rest and during work was normal, or even above normal.

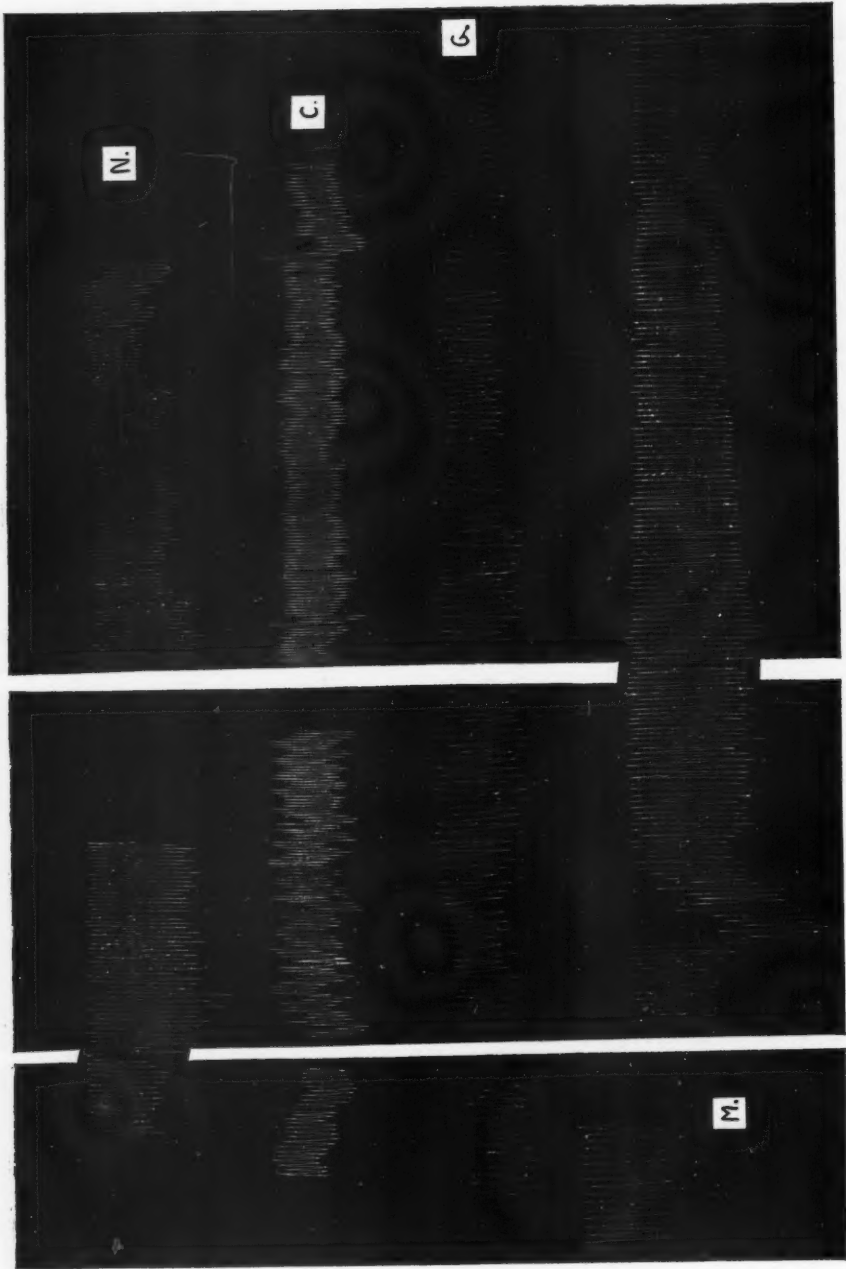


CHART IV. Drum records of the movements of the spirometer during (a) one minute's rest, (b) three minutes' exercise, and (c) five minutes' rest after exercise, which was 6 steps a minute for three minutes in each case except G., when it was 4 steps a minute. The drum was not run at the same rate, so the upper records have been divided so that the periods of exercise and of rest after exercise in each case start at the same point, which is shown by the broad white lines. The top record is a normal subject, the next is C., the next G., and the lowest M. Note that in M. the breathing is deeper, and in C. and G. considerably more shallow than in the normal. (For the explanation of the drop in the lowest record, see p. 53 in the following paper.)

The Relative Effect on Excess of Carbon Dioxide and Want of Oxygen on the Breathing.

In his recent book on Respiration, Haldane says: 'Speaking generally, the effect of excess of carbon dioxide is mainly to increase the depth of breathing and only slightly the frequency. On the other hand, anoxaemia produces a marked increase in frequency and only a moderate increase in depth' (18). This is now generally recognized, and has been carefully investigated by Haldane, Meakins, and Priestley (8, 9, 10), but its importance during exercise does not seem to have been realized.

The apparatus which we have used for measuring metabolism has shown itself very suitable for investigating this question, for if a subject breathes into the closed circuit without the soda-lime absorbers, the carbon dioxide will rapidly accumulate and there will be no lack of oxygen, provided the percentage was well above normal at the start. The tracing on the drum will show the effect with increasing percentages of carbon dioxide, and the depth rapidly increases and finally becomes very great, while the rate increases less quickly.

A second experiment of the same type shows the effect of the lack of oxygen without any accumulation of carbon dioxide, if the soda-lime absorbers are replaced in the circuit and the volume kept constant by admitting air instead of oxygen, so that the percentage of oxygen gradually falls. In this second experiment the depth is hardly increased at all, and the total ventilation only slightly when the 'breaking-point' is reached. If breathing into the apparatus is continued as long as it can be borne, the subjective sensations are also very different. With carbon dioxide accumulating, the sensation is not unpleasant, although great breathlessness is produced, and finally dyspnoea, tachycardia, and sweating. The general effect is rather like taking vigorous exercise. On the other hand, with increasing lack of oxygen, the sensation is very unpleasant; the pulse-rate is increased to a greater extent, palpitation is noticeable, and although the depth of breathing is hardly increased at all, and the rate much less than it often is in exercise, the subject feels unable to get his breath and has to stop, or is stopped by the observer because of his ashy colour. The figures for three normal men are given in Table VIII.

The Pulse-rate after Exercise.

The object of this paper is primarily a consideration of the breathing in bronchitis, but as the heart is so commonly affected it is necessary to decide whether there was evidence of cardiac involvement in these patients. Without actual measurements of the minute volume of the heart, one must rely on the clinical examination and on the rate of fall of the pulse after exercise to its value at rest.

Observations on the pulse-rate were made before and after the exercise and sometimes during it. In the subjects S. and B., during the first series, the rise in

(For the explanation of the start at the same point, which is shown by each record, see p. 53 in the following paper.)

pulse-rate and the fall to normal after 12 steps during one minute were within normal limits. In W. on the first occasion the pulse beforehand was 92, and for successive minutes after work was 112, 98, 96, i.e. abnormally high, but this was when he was at his worst, and a week later the result was within normal limits. In P. the fall in pulse-rate was perhaps a little slow, since the value for the second minute was 83, i.e. 9 beats above the resting value; in this case there were extra-systoles which are included.

In the second series (12 steps a minute for three minutes) the pulse of several normal controls had returned to within five beats of the resting value by the second minute after the exercise; B.'s pulse was perhaps a little slow in returning to rest after 18, but was normal after 12 steps. H. behaved normally at both rates of exercise. P., S., and W. were examined again at this rate in November 1925. S.'s pulse-rate was now 96, even at rest, but W. still gave a response which was within normal limits. Although P. seemed so much better and said he was hardly short of breath, the response of his pulse was just about the upper limit of what could be called normal.

A very large number of pulse-rates were taken in the last series. In C. the results were very variable, and on the first occasion only the pulse remained well above 100 for five minutes after the exercise. Five days later the value at rest was 70, and in successive minutes after exercise 86, 76, 76, 72, i.e. almost within normal limits, but on several later occasions the reaction was not nearly as good as this. In the case of M. the resting value was always low (between 60 and 68), and though the behaviour of the pulse after exercise varied, it had never returned to anywhere near the resting value by the second minute, since the value varied from 71 to 97, the highest value being obtained when he had to stop owing to pain in the chest. G., who died two years later, only managed 4 steps a minute, and his pulse remained strikingly high, i.e. 92-112 during the second minute; at rest it was always over 90.

Shortly, M., with myocardial degeneration, and G., who may have had this, showed a very abnormal response of their pulse-rate after exercise. W. and C. gave abnormal results when they were at their worst, but were within normal limits at other times. In B. the behaviour of the pulse was generally normal, but during and after the most severe exercise the rate was high, and perhaps it was just above normal limits in P., in whom extra-systoles were present. S. and H. (who was diagnosed 'effort syndrome') showed no difference from the less fit among the normal controls.

This analysis is important, since Peabody and Sturgis (17) have shown that in patients with valvular heart disease exercise causes an increase in the ventilation and a rapid and shallow type of breathing. It is interesting that rapid and shallow breathing also characterized our two bronchitic patients (S. and B.), in whom the heart's action was normal, as well as the others in whom the heart's action was rapid.

Discussion.

While a more detailed discussion is postponed to the next paper, there are three points that may be considered here. There seems to be a connexion between the length of the history of the disease and the rate of breathing. Subjects S., B., H., and C. all had very rapid respiration during and after exercise, and the duration of the disease was 6, 15, 6, and 10 years respectively. In P. and G., with a history of one month and eighteen months, the rate of respiration was not very much above normal. On the other hand, W., who had been ill for a year, showed during his acute attack a very high rate (44 during work), which as he recovered became much lower, particularly after exercise (Table IV), so that he seemed to belong to the latter group. Two years later, when the condition was becoming chronic, his rate of breathing appeared to be increased permanently.

Secondly, this rapid breathing, so long as it remains shallow, is less efficient in ventilating the lungs, because the dead space becomes of more significance and the true alveolar ventilation is less. This is one factor in increasing breathlessness. Its importance is shown by the following figures at rest: Assuming a dead space of 150 c.c., the alveolar ventilation in health was 5.5 litres, and in the breathless it was practically the same, so that the more shallow respiration was the essential factor in the increased pulmonary ventilation. During exercise the disadvantage of shallow breathing was even greater, as in the first series the average alveolar ventilation in health was just over 15 and in the breathless only 13 litres, assuming that there was no change in the dead space. However, it is possible that this effect of diminished alveolar ventilation may be counteracted to some extent by diffusion that must occur with shallow breathing, as described in the next paper.

When the exercise was continued for longer the depth of breathing increased, so that in the less severe cases the ventilation was much greater than normal and the true alveolar ventilation must also have been increased.

The third point is the vital capacity and the relationship of this to shallow breathing. Even in health dyspnoea results when the depth of breathing reaches a certain fraction (often about a third) of the vital capacity (5, 13, 20), and so, if it was much reduced in these subjects, one could not expect them to breathe nearly as deeply as usual without subjective symptoms. Recently emphasis has been laid on this as a cause of the sensation of breathlessness. In these patients the vital capacity was not observed continuously as a measure of their progress, but in S., B., and G., with chronic bronchitis, taken about the time of the early observations, it was 2.9, 2.9, 2.3 litres, i.e. 37, 32, and 45 per cent., below the expected values calculated from Dreyer's tables (15). In C. it was not observed, but the chest expansion was only half an inch, so it must have been very low. In the other two with chronic bronchitis it was taken two years later, and was 1.8 in P. and 1.9 in W., i.e. 55 and 54 per cent. below standard. In S. it was practically the same after two years. In H., with effort syndrome, it was 3.6,

and in M. with myocardial degeneration 4.0 litres, i. e. 17 and 15 per cent. below standard—practically normal figures when the fact that they were taking no exercise is considered. The great clinical improvement in P. was not accompanied by a return of the vital capacity to normal.

This does not suggest a very close parallel between reduced vital capacity and ability for exercise, but the results are interesting. M.'s deep breathing seems to be associated with his high vital capacity, but in H. this is not the case.

Means and Balboni (4) have investigated the respiratory response to carbon dioxide in subjects with artificial pneumothorax, which produces diminished vital capacity in its purest form. They found that the percentage increase in the ventilation corresponding to increasing values of the inspired carbon dioxide was normal; but that the respiratory rate was increased and the breathing became shallow. In the ambulatory cardiac patients examined by Peabody and Sturgis (17) the respiration was more shallow and more rapid than normal, and the vital capacity somewhat diminished.

We may take it then that many cardiac patients and patients with bronchitis show this type of breathing, and in all these the vital capacity is diminished, this being responsible partly for the shallow breathing. Want of oxygen certainly plays a part in many cases, and in a future communication we shall show that residence in an oxygen chamber slows and deepens the respiration of certain patients.

It was of interest to test the vital capacity at the end of an experiment, in which the subject had been breathing air containing a steadily diminishing quantity of oxygen, the carbon dioxide not being allowed to accumulate. Two experiments were carried out on Ca. When he was nearly at the breaking-point the expiratory tube was quickly removed from the circuit and attached to a spirometer. While this was being done, he took as deep an inspiration as possible from the impoverished air in the apparatus and expired fully through the meter. On both occasions his vital capacity was 4.5 litres, which was up to his normal figure and showed that the relatively shallow breathing from oxygen want was not associated with a diminishing vital capacity. Meakins and Davies have obtained the same result (24). Haldane, Meakins, and Priestley (8) have suggested that in effort syndrome derangement of the Hering Breuer reflex is the primary cause of the shallow breathing, and that this tends to oxygen want, which in itself keeps the breathing shallow, so that a vicious circle becomes established. Presumably in our bronchitic patients, the primary cause is in the lungs, and the respiratory centre is reflexly affected.

Although it is very likely that a diminished vital capacity may be an important factor in causing rapid shallow respiration we would emphasize the fact that a cardiac patient may be very short of breath and yet have practically a normal vital capacity. M. was a case in point; though his breathing always tended to be deep, he was one of the most breathless of our patients and could hardly walk up a flight of stairs without stopping.

Conclusions.

1. In men who are short of breath from chronic bronchitis and emphysema the pulmonary ventilation at rest is just above normal, but in practically every case the rate of breathing is more rapid and the depth less, so that the alveolar ventilation is about the same as in health.

2. Exercise causes rapid breathing in bronchitis. At first the breathing is shallow, later it increases in depth, though it still remains relatively shallow in the more breathless cases, so that the alveolar ventilation is relatively low.

3. In the breathless the return of the respiration to the resting condition is slower and less complete than normal; this is especially true of the rapid breathing.

4. Some evidence is brought forward that in chronic bronchitis the rapidity of respiration increases with the duration of the disease.

5. In some cases of bronchitis the pulse-rate is increased with exercise; but when the pulse-rate is normal the respiratory phenomenon still remains characteristic.

6. We have confirmed the fact that, in the normal, increase of carbon dioxide causes primarily an increase of respiratory depth, and defect of oxygen an increase in respiratory rate.

7. The vital capacity may generally be a big factor in controlling the depth of respiration, but severe breathlessness was seen in a cardiac patient with nearly normal vital capacity, whose respiration was deep.

8. One patient with effort syndrome behaved similarly to the patients with bronchitis of moderate severity.

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EFFECT OF EXERCISE ON THE PULMONARY VENTILATION 43

TABLE I.

Ventilation and Rate and Depth of Breathing in Breathless Subjects at Rest.

Subject.	Period.	No. of Observations.	Ventilation. (Litres.)		Rate of Breathing.		Average Depth (c.c.).
			Average.	Range.	Average.	Range.	
P.	March 1923	(4)	5.5	4.6-6.7	20	19-23	275
S.	March 1923	(4)	12.2	11.5-13.7	34	30-39	360
B.	March 1923	(7)	9.5	8.0-11.5	28	21-33	340
B.	June 1923	(2)	9.3	8.1-10.6	23	20-26	405
W.	June 1923	(3)	10.2	8.8-11.9	24	17-33	425
H.	June 1923	(3)	9.0	8.5-9.5	17	16-18	530
C.	February-April 1924	(7)	7.5	6.4-8.7	25	19-35	300
G.	February-April 1924	(4)	7.1	5.9-8.7	18	16-20	390
M.	February-April 1924	(9)	9.5	6.7-11.5	18.5	16.5-20	510
Average *			8.9	—	23	17-34	385
Normal	{ Maximum †		9.0	—	18	—	580
	{ Average		7.8	6.5-9.0	15	12-18	520
	{ Minimum †		6.5	—	12	—	370

* Excluding H. and M. because of their different pathology.

† Excluding one value for each already referred to in text.

TABLE II.

The Ventilation during Exercise in a Normal.

Rate of Exercise for three minutes.	Ventilation (litres).	Rate.	Depth (c.c.).
Rest	9.6	16	600
6 steps a minute	17.6	17	1040
12 steps a minute	21.8	18	1210
18 steps a minute	28.1	20	1400
24 steps a minute	40.0	26	1540

TABLE III.

Ventilation and Rate and Depth of Breathing at Rest and during One Minute's Exercise in Healthy and Breathless Subjects.

Subject and Number of Observations.	At Rest.			During Exercise.			
	Ventilation (litres).	Rate.	Depth (c.c.).	Ventilation (litres).	Rate.	Depth (c.c.).	
S. (4)	{ Max.	13.7	39	380	25.1	45	670
	{ Av.	12.2	34	360	23.5	38	620
	{ Min.	11.5	30	340	22.6	34	560
B. (7)	{ Max.	11.5	33	380	23.2	37	620
	{ Av.	9.5	28	340	17.5	29	560
	{ Min.	8.0	20	240	14.7	26	500
P. (4)	{ Max.	6.7	23	350	13.7	26	540
	{ Av.	5.5	20	275	12.0	25	480
	{ Min.	4.6	19	230	10.3	25	390
W. (6)	{ Max.	11.9	33	630	22.0	44	650
	{ Av.	9.5	19	500	17.4	34	510
	{ Min.	7.0	13	290	13.7	27	390
Normal (6)	{ Max.	8.8	17	580	19.4	26	1210
	{ Av.	7.8	14	520	18.0	19	950
	{ Min.	6.5	12	380	16.2	15	750

TABLE IV.

Effect of Exercise (12 Steps a Minute for 1 Minute) on Pulmonary Ventilation and Rate and Depth of Breathing.

Pulmonary Ventilation.

Subject.	Rest.	Exercise.	First 5 minutes after Exercise.				
S.	12.2	23.5	20.5	18.0	16.0	15.1	14.0
B.	9.5	17.5	18.5	17.5	13.9	12.4	12.0
P.	5.5	12.0	13.5	10.5	9.0	8.5	8.1
W.	9.5	17.3	15.3	13.0	10.5	10.7	10.9
Average	9.2	17.6	17.0	14.8	12.4	11.7	11.3
Normal Average (6)	7.5	18.0	17.5	10.0	9.5	9.0	8.0
Normal Fa.	7.5	19.3	16.0	11.4	10.5	9.4	9.4
Normal We.	6.5	19.4	18.4	12.2	11.4	10.3	9.7

Rate of Breathing.

S.	34	38	39	40	39	39	38
B.	26	29	32	37	36	36	35
P.	20	25	25	24	23	23	24
W.	19	34	29	23	23	23	24
Average	25	32	31	31	30	30	30
Normal Average (6)	14	19	19.5	17	17	17	14
Normal Fa.	13	16	20	21	21	20	15
Normal We.	17	26	21	20	19	19	17

Depth of Breathing.

S.	360	620	525	450	410	385	370
B.	365	600	575	470	385	345	340
P.	275	430	540	435	390	370	370
W.	500	510	525	565	440	465	455
Average	370	550	550	480	430	390	380
Normal Average (6)	535	950	850	590	560	540	560
Normal Fa.	580	1240	800	540	500	470	630
Normal We.	380	750	880	610	600	540	570

TABLE V.

Effect of Exercise (12 Steps a Minute for 3 Minutes) on Pulmonary Ventilation, and Rate and Depth of Breathing.

Subject.	Rest.	Pulmonary Ventilation.			After Exercise.				
		Exercise (3 mins.).							
		(1)	(2)	(3)	(1)	(2)	(3)	(4)	(5)
H. 1923	7.8	21.4	31.0	34.3	21.7	18.5	14.9	12.4	10.9
B. 1923	8.1	18.0	24.3	30.3	31.0	25.5	21.6	15.6	13.8
W. 1923	7.0	12.1	15.4	17.6	14.6	13.2	12.4	10.0	10.0
W. 1925	7.6	16.0	20.4	24.3	17.2	14.5	11.7	11.4	10.7
S. 1925	11.8	30.5	31.2	33.6	26.5	21.6	18.4	17.6	16.0
P. 1925	8.0	14.4	19.2	21.6	16.0	11.2	9.6	9.6	9.6
Patients' Average	8.4	18.7	23.7	27.0	21.2	17.4	14.8	12.8	11.9
Normals' Average (5)	8.7	15.4	17.7	19.4	14.3	11.1	10.3	9.6	9.1
Normal Max.	11.2	17.0	19.8	22.4	16.8	14.4	14.8	13.0	11.2
Normal Min.	6.9	12.3	13.9	13.8	11.2	9.4	8.2	7.5	7.5
<i>Rate of Breathing.</i>									
H. 1923	19	28	33	34	30	28	25	24	22
B. 1923	20	27	28	31	42	33	30	26	25
W. 1923	13	20	23	25	16	17	18	16	16
W. 1925	16	38	36	39	26	23	21	23	21
S. 1925	26	37	39	41	32	29	28	28	28
P. 1925	18	24	28	28	25	21	20	20	20
Patients' Average	19	29	31	33	28.5	25	24	23	22
Normals' Average (5)	16	17	18.5	19	17	16	15.5	16	16
Normal Max.	17	18	19	20	18	18	17	17	18
Normal Min.	16	16	16	17	16	14	14	15	13
<i>Depth of Breathing.</i>									
H. 1923	410	765	940	1010	720	660	595	505	495
B. 1923	405	665	870	970	740	770	720	600	550
W. 1923	540	505	670	705	920	780	690	925	625
W. 1925	475	420	520	620	660	630	560	500	510
S. 1925	460	820	800	820	880	740	650	620	570
P. 1925	440	600	680	770	640	530	480	480	480
Patients' Average	440	640	760	820	740	690	610	560	540
Normals' Average (5)	540	910	960	1020	840	690	660	600	565
Normal Max.	700	1010	1200	1290	1050	1030	980	770	680
Normal Min.	430	690	730	730	670	530	460	440	440

TABLE VII (*continued*).

Rate of Breathing.									
Subject.	Rest.	Exercise (3 mins.).			After Exercise.				
		(1)	(2)	(3)	(1)	(2)	(3)	(4)	(5)
G. (4 steps)	18	21	20	21	20	19	18.5	18.5	17.5
M. (4 steps)	18	22	22	24	21	20	21	21	21
Normal Cr. (4 steps)	12	14	12	12	15	14	14	13	12
M. (6 steps)	18.5	22	23	23	21	21	20.5	20	20.5
C. (6 steps)	25	28	31	31	28	28	28	27	27
S. 1925 (6 steps)	26	35	37	40	35	34	31	28	28
Normal Average (6 steps)	17	17.5	20	19	17	16.5	17	17	18
Normal He. (6 steps)	16	16	18	18	15	14	14	14	16
Normal Fr. (6 steps)	22	23	25	25	22	22	22	23	24
Normal Ch. (6 steps)	12	11	12	12	11	10	11	11	12
Normal Le. (6 steps)	19	20	25	22	19	20	21	19	21
Depth of Breathing.									
G. (4 steps)	390	390	450	475	465	410	405	390	410
M. (4 steps)	540	620	790	820	805	705	590	550	525
Normal Cr. (4 steps)	550	800	933	933	746	629	571	554	533
M. (6 steps)	510	700	850	940	940	805	680	630	560
C. (6 steps)	300	310	395	415	495	405	405	345	345
S. 1925 (6 steps)	460	590	620	600	500	490	495	460	460
Normal Average (6 steps)	440	685	690	750	680	560	505	495	455
Normal He. (6 steps)	494	742	721	790	740	614	636	636	557
Normal Fr. (6 steps)	382	638	643	657	614	500	473	448	412
Normal Ch. (6 steps)	582	1045	1220	1160	964	890	672	745	618
Normal Le. (6 steps)	348	500	464	555	590	440	358	332	305

TABLE VIII.

The Relative Effect of an Increasing Percentage of Carbon Dioxide and a Diminishing Percentage of Oxygen on Respiration and Pulse-rate.

Time in Minutes.	Carbon Dioxide Percentage increasing.				Oxygen Percentage diminishing.			
	Rate.	Depth (c.c.).	Ventilation (litres).	Pulse-rate.	Rate.	Depth (c.c.).	Ventilation (litres).	Pulse-rate.
Subject A.								
1	18	570	10.2	68	19	550	10.4	68
5	21	810	17.0	80	19	560	10.6	74
7	25	1160	29.0	90	—	—	—	—
9	25	1660	41.5	100	18	550	9.9	90
10	27*	1660	45.0*	104	—	—	—	—
12	—	—	—	—	21	560	11.8	96
15	—	—	—	—	21*	610	12.8*	114
Subject D.								
2	12	990	11.9	—	13.5	800	10.8	60
4	15	1100	16.4	—	—	—	—	—
6	21	1930	40.5	—	16.5	720	11.9	—
8	20	2920	58.2	—	15.5	700	10.9	—
10	22*	2760	61.0*	—	16	780	12.4	108
14	—	—	—	—	20*	840	16.4*	—
Subject K.†								
16	16	555	8.8	72	16	400	6.4	74
3	13	800	12.0	78	17	375	6.4	80
5	17	1780	30.4	82	17	375	6.4	84
7	16*	2500	40.0*	90	17	375	6.4	92
9	—	—	—	—	18	550	10.0	100
11	—	—	—	—	24*	500	12.0*	116

* Had to stop at this point.

† Results were produced more rapidly owing to a smaller volume of the circuit.

THE EFFECT OF EXERCISE ON THE RESPIRATORY EXCHANGE IN CHRONIC BRONCHITIS^{1, 2}

PAPER II

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THE general scope of this investigation has been described in the preceding paper and need only be summarized shortly. In the first series of observations three men with bronchitis (S., B., and P.) stepped on and off a thirteen-inch block twelve times in one minute, and their metabolism was followed before, during, and after this exercise. In the second series two men, one with bronchitis (B.) and one with effort syndrome (H.), did the same exercise for three minutes, and a smaller number of observations were made while they were doing eighteen steps a minute for three minutes; another man with asthma and bronchitis (W.) did twelve steps a minute generally for one minute only. In the third series the men were less fit; one with chronic bronchitis (C.) and one with myocardial degeneration (M.) stepped on and off the block using an intermediate step, six steps a minute for three minutes, and a third, with chronic bronchitis and probably myocardial changes (G.), was only able to do this four times a minute for three minutes. A few observations made later in 1925, mostly at twelve steps a minute for three minutes, have been added.

The changes in the pulmonary ventilation under these conditions have already been described, and the changes in metabolism will now be discussed. In the first series only the oxygen intake was measured; in the second the carbon dioxide output was sometimes measured as well, and in the third it was measured each time, so that the last series gives the most complete picture of the metabolic changes.

The metabolism was measured by means of a specially constructed closed-circuit apparatus. The oxygen intake and the pulmonary ventilation were read directly from dials. The percentage of carbon dioxide in the expired air was determined during the rest period at the beginning, and at two-minute

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³ Working under the tenure of a Beit Memorial Research Fellowship.

intervals during and after the exercise, beginning at the end of the first minute of exercise. The values at the end of alternate minutes were obtained by interpolation. The output of carbon dioxide for each minute was calculated from the pulmonary ventilation during the minute and the percentage of carbon dioxide at the end of the minute. Obviously the figures put for the output of carbon dioxide are not as accurate as those for the oxygen and the ventilation, but they may be used in comparison between breathless and healthy individuals examined in exactly the same way, and this applies to the respiratory quotients.

The metabolism was taken sitting at rest before starting the exercise, since some base-line was required to show the increase due to the exercise; as this was all that was needed, the basal metabolism was not measured. This last has been investigated in various types of breathlessness and is normal in compensated, and slightly raised in uncompensated cardiac patients (6). Where the breathlessness is due to chronic bronchitis, it is presumably not raised. In a recent review where a large number of patients with various diseases are discussed, bronchitis is not included as one of the rather small number of conditions where any abnormality of the basal metabolism has been found (20).

Total Oxygen Consumption during and after Exercise.

This was measured on each occasion, and the average results for each man at the various rates of exercise are shown in Table III, which gives the oxygen at rest, the 'extra' oxygen during each minute of exercise and during the five minutes' rest afterwards (reduced, as are all the other oxygen and carbon dioxide volumes in this paper, to normal temperature and pressure). It includes the average results obtained with normal subjects and individual observations from each end of the normal range. As the oxygen consumption at rest varied from day to day, this has been deducted from the oxygen consumption per minute during and after exercise and the result expressed as the 'extra' oxygen used. Observations on our patients were made before, during, and after oxygen treatment. In the third series the results for the oxygen consumption before oxygen treatment are alone used in this paper; but in the other two series the average of all observations is given, unless it was clear that oxygen treatment made a difference, in which case the figures before oxygen treatment are the only ones given.

Where the exercise lasted for three minutes the oxygen intake was generally a little higher in the third minute than in the second, so that equilibrium had not yet been reached. Longer experiments have shown that the exercise must be continued for five minutes, but in the third minute the healthy subject has very nearly reached equilibrium at these slow rates of exercise. The total extra oxygen used during and after exercise must be taken as a measure of the extra energy actually needed for the exercise, and the first point of interest is whether this is the same in the breathless subjects as in the healthy.

The 'extra' oxygen varies with the amount of work done, and this depends

on the weight, as the height of the step was the same for the normal and pathological. The external work done was 0.325 kilogrammetre per step per kilo of body-weight, as the height of the step was 32.5 cm.; to get the number of calories used this figure must be multiplied by 0.00235, since 1,000 kilogrammetres are equivalent to 2.35 calories (5). The oxygen needed for this energy will vary according to the respiratory quotient, but if this is 0.85, 1 litre of oxygen will give 4.83 calories (1), and if it is between 0.75 and 0.90, which will generally be true, the error involved in taking this figure is not much more than 1 per cent. Therefore the oxygen needed as the actual physical equivalent of the work done is 0.157 c.c. per step per kilo of body-weight.

Table I gives a summary of the results, column 5 expressing as oxygen the physical equivalent of the work (obtained by multiplying the total number of steps by the weight of the subject in kilos and by 0.157); column 6 giving the oxygen actually used in excess of the resting metabolism during the exercise and five minutes after; and column 7 the percentage 'efficiency' of the subject at the particular rate of work, i.e. the ratio of the oxygen equivalent of the work to the total 'extra' oxygen used. The average efficiencies for the third series have not been given in this table, because at this low rate of exercise the same patient gave greatly varying results from day to day.

Strictly speaking, the metabolism at rest should be taken standing instead of sitting, so that the difference would give the extra oxygen needed for the actual work of stepping, but this would have added greatly to the inconvenience of the breathless. Many of the normals were examined both ways, and the true 'efficiency', using the oxygen consumption standing as the base-line, was higher than the efficiency given here, i.e. it was about 17 or 18 instead of 15 per cent. But we are concerned only with the relative efficiency in men who are healthy or breathless; and all the results given are calculated by using the metabolism when sitting as the base-line.

Three things can be noticed in this table. The efficiency in the healthy was, with the notable exception of W., greater than in the men who were short of breath. The efficiency improved somewhat as the rate of work increased. The efficiency for this type of exercise was in all cases low compared with the usually accepted standard of 20-25 per cent. for many other rates of work (5, 14). The reason is that raising one's weight on to a step of this height is not a comfortable or economical form of work, partly because of the height and partly because of the stepping backwards and forwards, instead of going steadily upstairs in a more accustomed way. Stepping slowly is specially irksome to those not short of breath because the interval is long enough to settle down and a fresh start has to be made. Twelve or eighteen steps a minute was more comfortable, as a regular rhythm could be adopted; and breathing into the closed circuit at twenty-four steps a minute was quite within the power of the healthy. Without a mask or face-piece an ordinary man could easily do thirty steps a minute, and some few observations have been made at thirty-six steps a minute, but this rate of exercise could not be kept up for long. Even then local fatigue

of the leg muscle seems to be the limiting factor rather than the amount of ventilation or metabolism.

To give some idea of the difficulty of these stepping exercises compared with running or walking, the oxygen consumption needed is shown in Table II; six steps is slightly easier than walking $2\frac{1}{2}$ miles an hour, twelve steps about the same as $3\frac{1}{2}$, and eighteen steps as $4\frac{1}{2}$ miles an hour. The figures are for walking on a good surface, as Douglas found that the oxygen consumption for walking on grass was considerably higher (3). Except in the second series of observations, where the oxygen consumption was about $1\frac{1}{2}$ litres a minute, the subjects investigated were seriously limited by their breathlessness in the amount of exertion they were able to undertake. The lowered efficiency in the breathless subjects would limit to a small extent their capacity for exertion, but clearly it is a very small factor in the severe incapacity of a man only able to do six or twelve steps a minute.

Oxygen Consumption per Minute during and after Exercise.

On the whole, more extra oxygen was required for a given exercise by the breathless than by the healthy subjects, though the difference was not very great as judged by the efficiency figures. Differences were also found in the processes of adaptation at the beginning, and in the similar changes at the end of exercise. In the normal, various aspects of this question have been investigated by Krogh and Lindhard (4, 8), by one of the authors with Douglas and Hobson (14), by Hill, Long, and Lupton (19), and after exercise by Waller (7), the last less completely as he only measured the output of carbon dioxide. The changes observed by others need not be discussed fully here, because at each of the rates of exercise investigated healthy subjects have been examined for comparison with the breathless patients. The general reliability of this method, where the highest degree of accuracy is not needed, is confirmed by the agreement between what has been found by us in these normals and by the various workers already quoted.

In Table III the results at the different rates of exercise are given, and attention is drawn to the last column, which shows the percentage of the total extra oxygen that was taken up during the exercise. This value tended to be greater in the healthy than in the breathless patients, and the oxygen intake fell more rapidly to the resting value in the former.

In the first series (twelve steps in one minute) the results are irregular, particularly as far as the normals are concerned, probably because this time was too short for the oxygen intake to become steady. There was, however, a tendency for the oxygen intake in health to fall more quickly after the work, but W. again proved a notable exception.

In the second series (twelve steps a minute for three minutes) the proportion of extra oxygen absorbed by the normals during work was a little higher; but in the exercise eighteen steps a minute for three minutes the results were

practically the same. In B. the oxygen intake for the thirty-six steps fell a little, but not much more slowly than the normal. Curiously enough, the curve for H., the patient with effort syndrome, was almost identical with the curve for Sc., a remarkably fit man and a Rugby football player. (The normal subjects are denoted by two letters, e. g. Sc.; the breathless by one letter, e. g. S.). At eighteen steps a minute for three minutes there was not a big difference between the normals and our patients. In the practised subject Ca. the fall was quite rapid, but in Be. it was about the same as in H. or B.

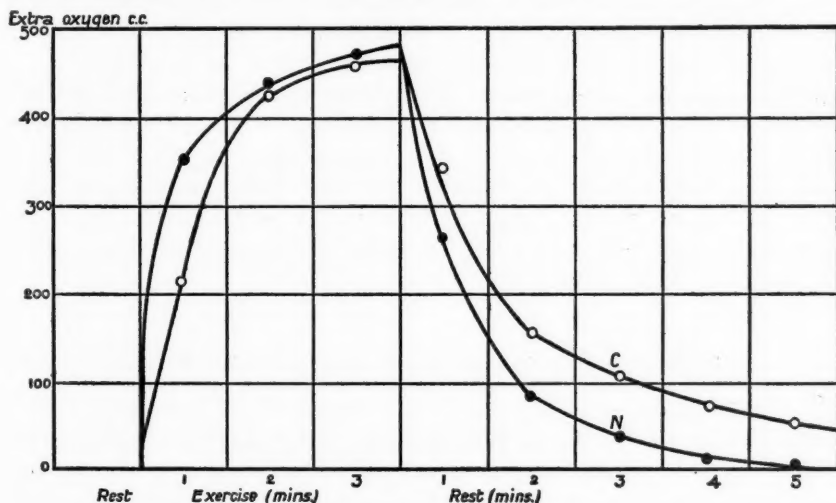


CHART I. 'Extra' oxygen used in normal (N.) and in one patient with chronic bronchitis (C.), during three minutes' exercise of 6 steps a minute and during each of the following five minutes. The oxygen intake in health rises slightly more quickly at the beginning of the work and returns to its resting value more quickly after. The oxygen intake of the bronchitic subject did not return to normal by the end of five minutes.

The following differences were obtained in the last series, where M. and C. could not do more than six steps a minute for three minutes. In the normal, 75 per cent. of the extra oxygen was used during work, though in Le., a normal who was not very fit, the proportion fell to 67. In C. it was 55, and in M. 55 per cent. The value for G. was 78 at a lower rate of exercise, and for the normal Cr. 84.5. In Chart I the average of all our results for the extra oxygen intake of C. is compared with the average normal, and in the latter the fall after exercise is the more rapid, and this is true for each of the normals individually, for their curves lie close together.

Most of the observations on M.'s oxygen consumption have been omitted from Table IV, as they were obviously too low because in his case, but not with any of the others, the level of the spirometer in the closed circuit rose, when he started to work, so that no measure of his real intake was obtained. This will be discussed in our third communication, and the average of two complete experiments in which it did not happen during oxygen treatment is shown

separately (Table III). The fall in extra oxygen intake at six steps a minute for three minutes was even slower than in the case of C. In 1925 S. showed a high oxygen intake for this rate of work, and not much, if any, delay in the fall afterwards.

So far we have said nothing about the rate at which the oxygen was absorbed during the work itself, when the exercise lasted for three minutes. On examining the individual curves we find that there is no significant difference between normals and patients as regards the rise in the oxygen intake from minute to minute during work, except in the last series of observations, where the rise in the case of C. and M. was slower than in three of our normals, and the rise in the case of G. slower than in the normal Cr.

To summarize our conclusions about the oxygen intake: there was little difference during the exercise; but after, especially in the subjects who were the most short of breath, the oxygen intake was generally higher and returned more slowly to its resting value than in the normal. This greater oxygen intake after the exercise led to a slight increase in the total oxygen intake with a slight decrease of 'efficiency', but this difference was not nearly great enough to account for the breathlessness.

The Output of Carbon Dioxide during and after Exercise.

The slower return to the resting value which was found in the breathless as compared with the healthy for the ventilation, and to a smaller extent for the oxygen intake, might also be expected to hold for the output of carbon dioxide. Actually as regards this the difference between healthy and breathless was more striking. Our most complete results were obtained in the third series. In Chart II is shown the output of 'extra' carbon dioxide for the bronchitic subject C. during and after exercise, consisting of six steps a minute for three minutes, and the figures for all three subjects are given in Table IV. During the first minute much less carbon dioxide left the body than normal, so there must either have been some retention or under-production of carbon dioxide. By the third minute of exercise C.'s output was still much below the average normal, and that there was some retention is well shown in the first minute after the exercise was stopped, when his output was considerably higher than in the last minute of exercise and only fell slowly. In the fifth minute after exercise the output of carbon dioxide was 234, although it started at 182; while in the healthy it was only 255, although it started much higher, at 230 c.c. per minute. The curve shown for C. in Chart II, and the figures here discussed, are the average results of six observations made at various times in the course of two months. In the case of M., with myocardial disease, the carbon dioxide was higher, presumably because of the greater work performed owing to his greater weight. The more gradual rise in the output of carbon dioxide and the much more gradual fall were shown in just the same way, but there was not so much retention during work. The rate of fall after the first minute of rest was about the same as for C.

Results of the same sort were found with the other bronchitic subject G., and with S. when he was re-investigated two years later.

These results are given in detail in Table IV, but the smaller number of determinations of carbon dioxide output at the more rapid rates have not been given in full, because generally they were the results of single observations.

We have some results for B. and H. and the normal Be., obtained during the second series of observations at eighteen steps for three minutes. During this work the rise in carbon dioxide output between the first and third minute was about the same in all three cases, but the fall in carbon dioxide after the work was slower in the case of B. than in H. and the normal Be., as the following figures

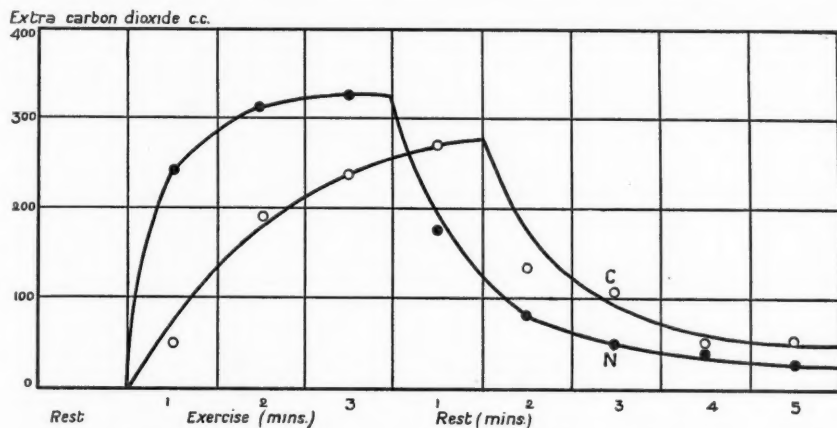


CHART II. 'Extra' carbon dioxide output in normal (N.) and in the same patient with chronic bronchitis (C.) during the same period as Chart I. In health the output of carbon dioxide rises more quickly at the beginning of exercise and falls much more quickly afterwards.

for the extra carbon dioxide of these subjects during the third minute of work and the second, fourth, and seventh minutes after work show, viz.: B. 1,065, 693, 182, 64 c.c., H. 1,170, 495, 80, 9, Be. 1,060, 287, 165, 14 c.c.

Some results at twelve steps a minute for three minutes obtained in 1925 are also given here. The extra output of carbon dioxide in the third minute of exercise, and in the second, fourth, and sixth minutes after stopping, was for W. 660, 327, 164, and 68 c.c. per minute; for S. 790, 292, 138, and 68 c.c.; and for the normal Sa. 697, 177, 64, and 34 c.c. W. shows a more gradual fall than the other two.

Respiratory Quotient.

This is always difficult to analyse because it is the resultant of so many factors, i. e. there may be an alteration in the true metabolism, or the apparent quotient may not correspond to the true metabolic one owing to the retention or subsequent expulsion of carbon dioxide. This has been discussed by Campbell,

Douglas, and Hobson (14). Generally when exercise is severe it will rise, owing to an increasing use of carbohydrate, to a rise of temperature, and to the production of lactic acid with the consequent expulsion of carbon dioxide; the exercise here studied was not of this degree of severity.

Against these factors tending to raise the quotient is the retention of carbon dioxide during exercise, with rise of partial pressure owing to its solubility in the body fluids. This will produce an apparent fall in the quotient which should be observable, if the metabolism is followed minute by minute during work. A fall in quotient might also be produced by some qualitative alteration in metabolism, e.g. the formation of carbohydrate from fat.

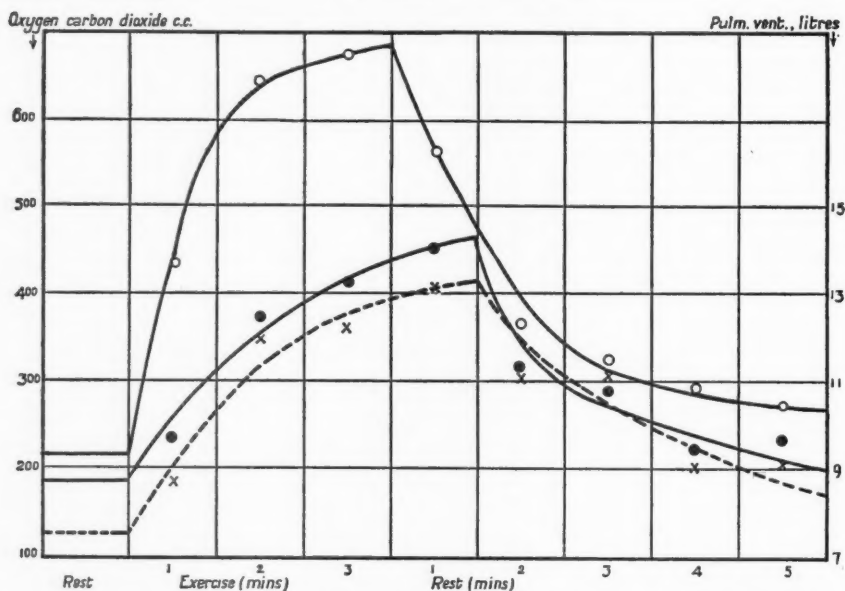


CHART III. Oxygen intake (o) and output of carbon dioxide (●) in a chronic bronchitic (C.) during three minutes' work of 6 steps a minute and five minutes after. During the exercise the two lines diverge, i. e. the quotient is low, and this occurs more in the breathless than in the healthy (see Chart IV). The interrupted line represents the pulmonary ventilation (x), which corresponds more closely with the carbon dioxide output than with the oxygen intake.

Figures for the quotients of the patients G., C., and S. (1925) are alone available (Table IV) because with M. the oxygen intake during exercise could not be measured accurately. At rest it was normal in these subjects, but very low quotients were obtained during exercise. However, generally within a minute of the rest period it had risen again to the original value, and in the following minutes higher values were always obtained, though only in the case of G. were they above unity. The quotients of the four normal subjects at six steps a minute also fell during exercise, but nothing like to the same extent. Thus the average fall during exercise was in the case of C. 0.28, and in the normals 0.07. After the exercise was over the quotient rose in the healthy above the

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resting value, the highest value in three of our normals being observed not later than the third minute after work, as found by Campbell, Douglas, and Hobson (14). The contrast between C. and the normals is illustrated by Charts III and IV. Table IV also shows that the rise in quotient after exercise over its value during exercise is much greater in the bronchitic than in the healthy subject. Such a rise must be either due to a relatively smaller intake of oxygen or to a larger output of carbon dioxide. But we have seen that there was certainly no abnormally rapid fall in the oxygen after exercise; rather the reverse. Hence

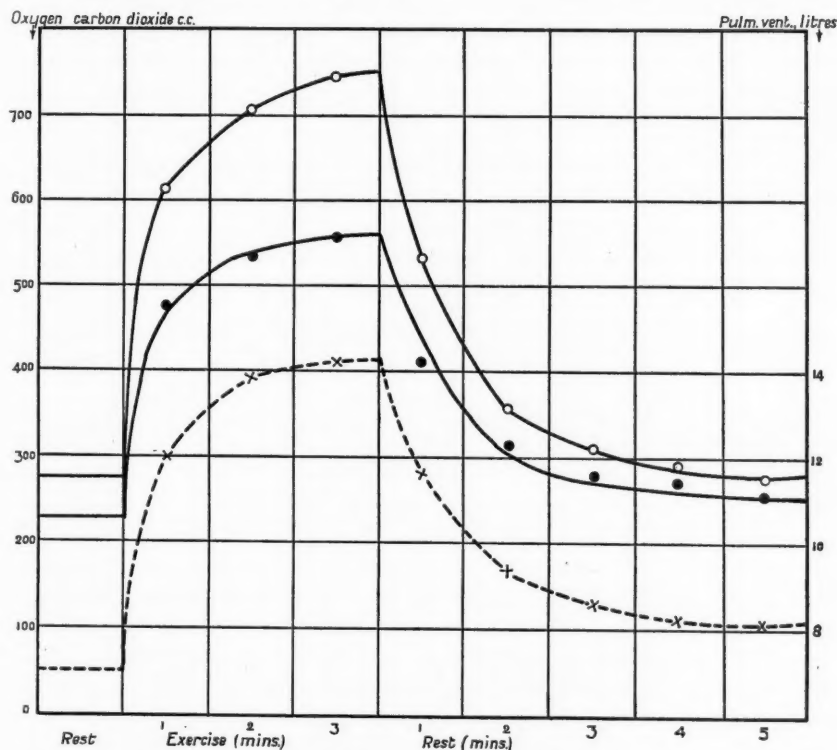


CHART IV. Average oxygen intake (o), and carbon dioxide output (●) and ventilation of four normal subjects for comparison with Chart III.

there must have been after work a still larger output of carbon dioxide, which is another way of illustrating the fact that the output of carbon dioxide fell more slowly than the intake of oxygen, after the work was completed. Further light is thrown on the subject by calculating the respiratory quotient from the 'extra' oxygen and 'extra' carbon dioxide, i.e. the quotient due to the work itself. For this purpose it is of course necessary to use the figures for the period of exercise and for the period of rest (sometimes ten minutes) until the metabolism falls again to its original level. Calculating in this manner, we have found that in the case of our patients G., C., and S. (1925) the quotient due to the work was

respectively 0.49, 0.62, 0.67, while in the four normals of Table IV it was 0.74, 0.96, 0.88, and 0.81.

It might be suggested that these strikingly low values in our breathless patients were due to a retention of carbon dioxide with a very slow evolution some time afterwards. While many observations were not carried on beyond the first ten minutes of rest, we have three results with C. and one with G. carried on for another five or ten minutes. With G. the quotient did rise decidedly above the resting value, and for the work it was certainly high; but with C. this was not the case. We are inclined to believe that, with C. at any rate, there was some qualitative alteration in the metabolism, and this view is further supported by the striking alteration of the quotient that occurred in his case with oxygen treatment. It is quite certain that fat must be utilized for the

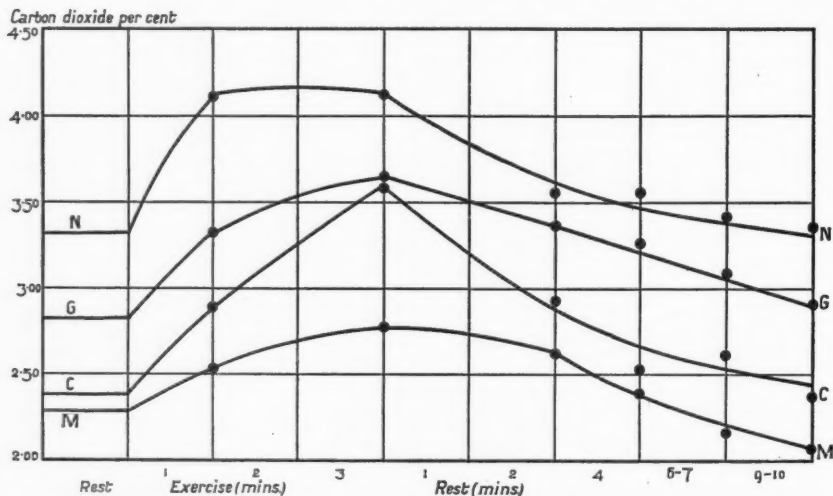


CHART V. Percentage of carbon dioxide in the expired air during three minutes' exercise at 6 steps a minute and subsequently. G., C., and M., breathless patients; N., average normal curve.

performance of muscular work, even though its use may be secondary and confined to the replenishing of the carbohydrate stores of the body, which are primarily drawn upon. The low 'work quotient' in our breathless patients might be due to an increased formation from fat of some more highly oxygenated compound.

The Carbon Dioxide Percentage in Expired Air.

In all these men the carbon dioxide percentage in the expired air was lower than the average in health, and this was true during exercise as well as at rest. In Chart V the curve showing the changes in the expired air of the three men of the third series is compared with the average curve for four healthy subjects. The latter is higher throughout, although the individual curves for the

breathless subjects are very different. The figures of individual cases are given in Table V, and Le., who gave the lowest normal figure, was rather unfit. The second striking fact about the normal curve is that the maximum percentage is reached practically in the first minute of exercise. In only one of the five normals of the third series was there a rise of as much as 0.26 per cent. between the first and third minute of exercise, while C. showed a rise of 0.66, G. of 0.33, M. of 0.25, S. (1925) of 0.23. It required an exercise of eighteen steps a minute for three minutes to produce a rise of 0.55 per cent. in a healthy subject.

The Percentage of Inspired Air absorbed in the Form of Oxygen.

This is obtained by dividing the percentage of carbon dioxide in the expired air by the respiratory quotient, or by calculating the volume of oxygen absorbed as a percentage of the pulmonary ventilation (the latter reduced to normal temperature and pressure). A few examples are given in Table VI. When the pulmonary ventilation during exercise was excessive, as was the case with H. and B. at twelve steps a minute, the percentage absorbed was lower than normal. However, in the very breathless subjects, when the pulmonary ventilation was, if anything, reduced, the percentage was about normal.

Discussion.

It is impossible from our present data to give a complete explanation of the cause of breathlessness in these patients, but we can briefly consider various possibilities.

Perhaps the most striking result obtained was the low percentage of carbon dioxide in the expired air. This has been described before (2, 11), and was found in all the patients previously investigated by us with G. H. Hunt (17). Briggs (12) found that the trained man was able to produce a higher percentage of carbon dioxide in his expired air during exercise than the untrained, and that breathing oxygen made no difference to the trained man (unless the work was extremely severe), while it enabled the man who was less fit to increase the percentage of carbon dioxide in the expired air, and so to get rid of a larger amount with a smaller ventilation. This suggests that in some way the difference between the trained and untrained is the same as the difference between those who are healthy and those who are breathless from disease. In our patients residence in oxygen raised the carbon dioxide percentage during work.

If shallow breathing is carried out voluntarily by a healthy man, the percentage of carbon dioxide in the expired air will of course be lowered, because to obtain the same effective alveolar ventilation a larger pulmonary ventilation will be required. Assuming a constant dead space, it is easy to calculate the theoretical increase in pulmonary ventilation as the breathing becomes shallower. Another possible factor must arise in shallow breathing which would tend to make such theoretical values too large, and also counteract the tendency to want of oxygen

described by Haldane, Meakins, and Priestley (9). This is the increased rate of diffusion that must occur between the ends of the bronchi and the alveoli as the bronchiolar air approximates more closely in composition to the atmosphere.

In most of these patients the breathing tended to be rapid and shallow, but this will not explain the low percentage of carbon dioxide in the expired air, because the lowest values of all were obtained with M., whose breathing was actually deeper than normal. Further, with H. and B. during the third minute of work at eighteen steps a minute the depth was practically normal, and yet the percentage was low.

There would seem to be only four possible explanations :

1. The presence of fixed acid such as lactic acid in the blood; this would cause increased respiration with a lowering of the pressure of carbon dioxide in the blood and tissues, and consequently a low percentage in the expired air. However, Campbell, Hunt, and Poulton (17) found no increase of fixed acid in this type of subject at rest, and a sudden formation of lactic acid during work might be expected to lead to a high quotient and carbon dioxide percentage, and neither of these were found.

2. Primary over-ventilation. This will cause a lowered pressure of carbon dioxide and lowered hydrogen-ion concentration in the arterial blood. On Pearce's theory, which is discussed later, this is a mechanism which in part compensates for a failing heart.

3. Resistance to the excretion of carbon dioxide, so that a steeper gradient is required between its pressure in the blood and in the alveolar air for its elimination to be possible. The resistance may arise from a decrease in the absorbing surface, as in emphysema, or from constriction of the bronchioles, preventing the escape of carbon dioxide from the deeper recesses of the lungs.

4. A lessened output of carbon dioxide. This might help in certain cases, but cannot be the main cause.

Pearce (15) has explained cardiac dyspnoea as follows : Retardation of the blood-flow causes accumulation of carbon dioxide and defect of oxygen in the veins of the respiratory centre, and hence in the centre itself, which as regards gaseous content is considered as being in equilibrium with the blood that leaves it. Stimulation of the centre results in increased pulmonary ventilation. The carbon dioxide in the alveolar air and arterial blood is lowered, so that its accumulation at the centre becomes less. The increased ventilation compensates for the slow circulation as regards carbon dioxide, but not as regards the oxygen, because in the latter case increased ventilation can produce very little increase in the oxygen pressure of the arterial blood.

In a series of ambulatory cardiac patients examined by Peabody and Sturgis the effect of exercise was to cause a bigger increase in the ventilation than normal, while the percentage of carbon dioxide in the expired air was abnormally low (16). These results fit in exactly with Pearce's theory. Our very breathless patient M., suffering from myocardial degeneration, also showed great increase in ventilation during exercise, while the maximum percentage of carbon dioxide during exercise

was very low, viz. 2.82, the normal value being 4.08. His breathing was deep and not very rapid, and the vital capacity (discussed in the last paper) was nearly normal. His breathlessness would be explicable on Pearce's theory, because our figures indicate that there was great delay in the output of carbon dioxide. For instance, during the first minute of work (at six steps a minute), in spite of a ventilation of 15.4 litres, the output of carbon dioxide was only 376 c.c., while in the normal with a ventilation of only 12 litres this output was 475 c.c. The output was low in spite of this high ventilation, so that obviously this patient was over-breathing.

A slow circulation may be compensated for as regards the accumulation of carbon dioxide by increased respiration; but it is possible to extend the theory to cover the condition of a primary defect in ventilation. Campbell, Hunt, and Poulton have observed a rise of carbon dioxide pressure and fall of oxygen saturation of the arterial blood in cases of primary lung disease. Given an impoverished arterial blood it would be of obvious advantage to the organism if the circulation rate were increased, since this would prevent any big difference between the arterial and venous blood from occurring, and it would keep the oxygen pressure in the tissues high, and carbon dioxide pressure as low as possible.

Is there any evidence that respiratory obstruction causes an increase in the minute volume of the heart? Such an increase has actually been found by Eppinger, Papp, and Schwartz (18) in cardiac asthma, which is one of the conditions in which Campbell, Hunt, and Poulton found an increase of carbon dioxide pressure and lowered oxygen saturation in the arterial blood. The slow return of the pulse to normal after exercise observed at different times in all but two of our bronchitic subjects also suggests a close connexion between circulation and embarrassed respiration, and it may well be that the rapid pulse means that there is a true increase of circulation to compensate for deficient respiration.

Reviewing all these results on bronchitic patients, we may point to the rapid and shallow breathing present in all of them as another characteristic way in which they react to exercise. However, as regards pulmonary ventilation, they fall into two groups. Characteristic of one group are B. and S., who, in the later stages of exercise, had a very much higher ventilation than normal (although when this ventilation was at its maximum the breathing was quite deep). In the other are the two very breathless subjects C. and G., whose pulmonary ventilation was below normal. In the first group the rate of absorption of oxygen during and after the work was practically normal, though there was a delay in the excretion of carbon dioxide as shown by the slow fall after the work. In the second group the absorption of oxygen was delayed, and the excretion of carbon dioxide very much delayed.

It follows that in bronchitis when the breathlessness is slight the respiration is stimulated, so that a very large ventilation results; this takes place first by increasing the rate and, later, also the depth of breathing. Thus the exchange of gases is fairly efficiently carried out. When the breathlessness is severe, the

rate of breathing remains high, but the depth hardly increases, consequently the pulmonary ventilation becomes less than normal, and the absorption of oxygen, and still more the excretion of carbon dioxide, is very much delayed.

It is difficult to see how acute bronchitis can cause breathlessness, except by producing a narrowing and blocking of the bronchioles and so introducing the element of resistance to respiration. This factor will also be present in chronic bronchitis, but emphysema causing reduction in the area for gaseous exchange is an additional cause.

Respiratory obstruction may, in itself, lead to modifications in the breathing, as has been shown by Davies, Haldane, and Priestley (10). With a normal subject the introduction of an artificial resistance to respiration leads at first to slow, deep breathing, and, after some time, to rapid, shallow breathing, which arises more quickly if there is want of oxygen as well as increased resistance. They consider that this change to rapid, shallow breathing means that the respiratory centre is becoming fatigued. We may also explain our results with C. and G. on these lines, since there was almost certainly considerable bronchial obstruction, as shown by the presence of high-pitched rhonchi throughout the lungs. The diminished ventilation which was found, in spite of the stimulating effect of carbon dioxide retention and oxygen want, is explained by the respiratory centre or possibly the respiratory muscles becoming fatigued. Direct evidence of this has been produced by allowing subjects of this type to breathe carbon dioxide, the resulting increase in the ventilation being less than normal (4, 13).

However, Haldane and his co-workers have pointed out that the rapid, shallow type of breathing itself tends to aggravate the want of oxygen, so that a vicious circle becomes readily established. They have explained the changes incidental to the failure of the respiratory centre as due to resistance, but our case C., at any rate, shows that this condition may be tolerated for some months or possibly for years.

We have not met clinically the condition described by Davies, Haldane, and Priestley as the first stage in respiratory obstruction, viz. slow, deep breathing, but patients with laryngeal diphtheria may react in this way. It is very unlikely that bronchial obstruction was a prominent feature in the case of B., because his ventilation during work was so greatly increased. Exactly similar breathing was noticed in H., with effort syndrome, which suggests that the breathing may be compensatory to an inefficiently acting heart on Pearce's theory. Again, B. was very emphysematous, and since a lack of surface over which an exchange of gases can take place would be compensated for by an increased ventilation, his modified breathing may be due to this cause. Perhaps the latter is the most likely hypothesis, and, on this view, we can readily see how it is that from the respiratory point of view patients with bronchitis fall into two groups. If emphysema is present without asthma the ventilation will be increased; but if asthma is present this will be impossible, and the patients will suffer from accumulation of carbon dioxide and oxygen want. In both groups the response of the respiration to exercise is the exact converse of the normal, since the rate of breathing

is increased at first, while it is only later that the breathing increases in depth though in the second group such an increase is hardly possible at all.

Finally, our results show that the pulmonary ventilation runs more parallel with the carbon dioxide output than with the oxygen intake. This is shown in striking figures in Case C. (Chart III), where both pulmonary ventilation and carbon dioxide output reach the maximum after the work is over and considerably later than the oxygen intake. Chart IV shows the average normal curves for comparison. Oxygen, carbon dioxide, and ventilation all run parallel to one another.

Conclusions.

1. Men who are very short of breath from chronic bronchitis and emphysema use rather more oxygen for the same amount of work than healthy men, but this difference is much too small to be an appreciable factor in their breathlessness.

2. Rather more of the oxygen used is obtained after the exercise is finished, which means that at the end of exercise there is a greater oxygen debt than normal. At the end of exercise the oxygen intake returns more slowly to its resting value in these subjects.

3. The carbon dioxide output shows a slower rise during exercise than normal, and a much more gradual fall to the resting condition is found afterwards. The divergence from the normal is much greater in the case of the carbon dioxide than the oxygen.

4. At rest, and during and after exercise, the percentage of carbon dioxide in the expired air of these patients is invariably lower than in health. This inability to produce a higher concentration of carbon dioxide may, perhaps, be regarded as the essential factor in the breathlessness. The relative importance of respiratory and circulatory disturbances in this connexion has been discussed.

5. In bronchitis the respiratory centre responds to the stimulus of exercise by rapid breathing. At first it is shallow, later on it may either become deep or remain shallow. It is suggested that the first occurs when there is emphysema but no asthma, and the second when asthma predominates. In this case the gaseous exchange is very inefficient.

6. Changes in the pulmonary ventilation follow more closely changes in the carbon dioxide output than the oxygen intake.

7. In myocardial disease the gaseous exchange may be very poor in spite of deep breathing. This is presumably due to primary circulatory insufficiency.

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TABLE I.*

Extra Oxygen Consumption and 'Efficiency' of Muscular Work in Men who are Healthy and Breathless.

(1) Subject.	(2) Weight (kilos).	(3) No. of Steps per Minute.	(4) Total Steps.	(5) Equivalent O ₂ . (c.c.).	(6) Extra O ₂ . (c.c.).	(7) Efficiency (per- centage).
S.	76.5	12	12	143	1400	10.0
B.	79	12	12	143	1930	7.7
W.	64	12	12	120	728	16.5
Normal Average (6)	69	12	12	129	1063	12.1
H.	68	12	36	382	3627	10.5
W. (1925)	64	12	36	360	3109	11.6
B.	79	12	36	443	3586	12.4
Normal Average (3)	71.5	12	36	404	2707	14.8
Normal Sch.	79	12	36	446	3310	13.4
Normal Hu.	63	12	36	356	2338	14.9
H.	68	18	54	575	4188	13.7
B.	79	18	54	668	5040	13.2
Normal Average (3)	74	18	54	628	4071	15.4
Normal Ca.	72	18	54	610	3831	16.0
Normal Be.	76	18	54	645	4705	13.7
Normal Ca.	72	6	60	678	5170	13.1
" "	72	12	36	407	2632	15.4
" "	72	18	54	610	3735	16.1
" "	72	24	72	814	4932	16.3
" "	72	30	90	1017	6300	16.1

* In this and the following tables, the oxygen intake and the output of carbon dioxide have been reduced to normal temperature and pressure.

TABLE II.

Oxygen Consumption in Various Forms of Exercise.

Exercise.	Oxygen Consumption (c.c. a Minute).	Observer.
Resting (bed)	240	(a)
Resting (sitting)	260	(d)
Resting (standing)	330	(a) (d)
Walking 2 miles an hour	670	(a) (b)
Stepping 6 steps a minute	780	(d)
Walking 3 miles an hour	910-950	(a) (b)
Stepping 12 steps a minute	1080	(d)
Walking 4 miles an hour	1180-1450	(a) (b)
Stepping 18 steps a minute	1520	(d)
Easy work on bicycle	1700	(c)
Stepping 24 steps a minute	1940	(d)
Walking 5 miles an hour	2130-2350	(a) (b)
Moderate work on bicycle	2300	(c)
Stepping 30 steps a minute	2400	(d)
Running 6 miles an hour	2700	(b)
Severe work on bicycle	2800	(c)
Running 7 miles an hour	3100	(b)

(a) Douglas (3).

(b) Hill, Long, and Lupton (19).

(c) Campbell, Douglas, and Hobson (14).

(d) This series.

TABLE III. *Extra Oxygen during and after Various Rates of Exercise.*

Subject.	Oxygen (c.c. per Min.) at Rest.	Extra Oxygen (c.c. per Minute).					Total Extra Oxygen.		Percentage of Extra Oxygen used during Exercise.	
		During Exercise.		After Exercise.			During Exercise.	10 Minutes after Exercise.		
		(1)	(2)	(3)	(1)	(2)				(3)
<i>12 steps a minute for 1 minute.</i>										
S.	339	773	—	—	434	191	5	0	0	
B.	370	613	—	—	784	238	114	57	81	
P.	260	649	—	—	592	124	2	0	0	
W.	283	434	—	—	257	47	0	0	0	
Bronch. Average	318	617	—	—	517	150	30	14	20	
Normal Average (6)	338	536	—	—	291	103	66	19	10	
<i>12 steps a minute for 3 minutes.</i>										
H.	236	575	688	999	641	386	226	56	56	
W. (1925)	266	605	721	746	418	276	181	70	42	
B.	284	360	778	882	740	380	123	76	47	
Normal Average (3)	292	368	651	783	547	156	90	47	38	
Normal Sch.	311	349	820	1009	679	302	141	10	0	
Normal Hu.	236	377	660	707	471	47	24	24	0	
<i>18 steps a minute for 3 minutes.</i>										
H.	232	534	832	1137	773	457	302	23	23	
B.	281	656	1312	1405	1215	375	57	0	0	
Normal Average (3)	301	545	1033	1155	873	235	122	47	38	
Normal Ca.	272	762	1042	1136	667	103	56	10	10	
Normal Be.	338	629	1052	1333	1146	347	160	28	9	
<i>4 steps a minute for 3 minutes.</i>										
G.	209	274	296	389	113	44	30	9	1	
Normal Cr.	300	347	300	284	162	69	0	0	0	
<i>6 steps a minute for 3 minutes.</i>										
C.	215	219	426	456	346	152	108	71	56	
S. (1925)	315	439	577	620	406	156	110	67	25	
M.*	255	264	420	424	420	132	108	71	42	
Normal Average (4)	275	351	431	469	265	81	38	14	10	
Normal Ch.	334	467	477	473	188	93	0	0	0	
Normal He.	275	341	484	503	351	76	28	9	0	
<i>1328</i>										

* Average of two experiments during oxygen treatment which are probably accurate (see text).

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TABLE IV.

Oxygen Intake, Carbon Dioxide Output, and Respiratory Quotient during and after Exercise of 6 steps a Minute for 3 Minutes.

Subject.		Rest.	Exercise.			Rest after Exercise.				
			(1)	(2)	(3)	(1)	(2)	(3)	(4)	(5)
G.*	CO ₂	199	252	309	341	295	256	247	234	227
	O ₂	209	483	505	598	322	253	239	218	210
	R. Q.	0.96	0.52	0.61	0.57	0.93	1.01	1.03	1.07	1.08
Normal Cr.*	O ₂	325	700	650	600	500	400	300	300	300
M.	CO ₂	196	376	495	560	494	398	326	283	258
	O ₂	231	422	—	—	—	—	—	324	256
	R. Q.	0.84	0.89	—	—	—	—	—	0.87	1.01
C.	CO ₂	182	287	372	418	451	316	291	229	234
	O ₂	215	434	641	671	562	367	323	295	271
	R. Q.	0.85	0.55	0.58	0.62	0.80	0.86	0.90	0.78	0.86
S.† (1925)	CO ₂	270	501	584	642	465	436	370	304	291
	O ₂	315	764	892	935	721	468	425	382	340
	R. Q.	0.86	0.65	0.66	0.68	0.65	0.93	0.87	0.80	0.85 ‡
Normal Average	CO ₂	230	475	538	555	412	311	279	269	255
	O ₂	276	616	706	744	538	358	312	290	274
	R. Q.	0.83	0.77	0.76	0.74	0.76	0.87	0.89	0.92	0.93
Normal He.†	CO ₂	225	442	538	555	384	268	295	300	302
	O ₂	275	616	758	778	626	351	303	284	265
	R. Q.	0.82	0.72	0.67	0.72	0.62	0.76	0.97	1.05	1.13
Normal Fr.†	CO ₂	230	553	602	602	439	340	267	266	229
	O ₂	243	582	660	683	465	332	303	274	238
	R. Q.	0.94	0.95	0.91	0.88	0.94	1.02	0.88	0.97	0.96
Normal Ch.†	CO ₂	292	564	664	678	480	366	326	313	301
	O ₂	334	801	811	807	522	427	332	332	332
	R. Q.	0.88	0.70	0.81	0.84	0.92	0.86	0.98	0.94	0.91
Normal Le.†	CO ₂	174	341	381	384	349	270	226	196	186
	O ₂	251	465	597	711	541	323	313	270	270
	R. Q.	0.70	0.73	0.64	0.54	0.65	0.83	0.72	0.73	0.69 ‡

* 4 steps a minute for 3 minutes only.

† These results are less regular as they represent single determinations, but where the oxygen results were very irregular from minute to minute they have been smoothed.

‡ High R. Q. was found in second 5 minutes.

TABLE V.

Carbon Dioxide Percentage in Expired Air.

Subject.	Rest.	Exercise.		Rest.			
		1st Min.	3rd Min.	2nd Min.	4th Min.	6th or 7th Min.	9th or 10th Min.
12 steps a minute for 3 minutes.							
W. (1923)	2.74	3.12	—	3.03	2.43	2.41	2.45
W. (1925)	2.35	3.33	3.72	3.59	3.37	2.70	2.34
S. (1925)	2.28	—	3.19	—	2.34	—	2.27
P. (1925)	2.76	—	3.20	3.49	2.95	2.81	2.76
Normal Sa. (3 obs.)	3.12	4.27	4.38	3.68	3.56	3.39	3.33
18 steps a minute for 3 minutes.							
H.	3.16	3.52	4.10	3.10	2.81	2.92	3.01
B.	2.58	3.91	4.10	2.95	2.80	2.60	2.53
Normal Be.	4.05	4.77	5.32	4.61	4.30	3.97	4.06
Normal Ca.	3.37	4.49	4.88	3.66	3.40	3.42	3.51
6 steps a minute for 3 minutes.							
C. (4 obs.)	2.38	2.90	3.56	2.93	2.53	2.61	2.37
M. (6 obs.)	2.29	2.53	2.78	2.64	2.40	2.16	2.08
G. (3 obs.)*	2.82	3.34	3.67	3.37	3.26	3.06	2.93
S. (1925)	2.28	2.44	2.67	2.60	2.44	2.21	2.37
Normal Average	3.31	4.11	4.11	3.59	3.55	3.42	3.36
Normal Ch.	4.43	5.19	4.98	4.34	4.32	4.24	4.10
Normal Fr.	2.90	3.75	3.76	2.99	2.82	2.96	2.88
Normal Le.	2.78	2.60	3.32	3.34	3.10	3.38	3.20
Normal He.	3.06	4.00	4.16	3.50	3.56	3.09	3.12
Normal Sa. (5 obs.)	3.39	3.99	4.25	3.69	3.48	3.45	3.41

* 4 steps a minute only.

TABLE VI.

Percentage of Inspired Air absorbed in the Form of Oxygen.

Subject.	Rest.	Exercise.		Rest. 2nd Min.
		1st Min.	3rd Min.	
<i>12 steps a minute for 3 minutes.</i>				
H.	3.2	4.0	3.8	3.6
B.	3.7	3.8	4.1	2.7
Average Normal	3.6	4.6	5.9	4.2
<i>6 steps a minute for 3 minutes.</i>				
C.	3.0	5.6	6.1	3.6
Average Normal	4.2	5.6	5.9	4.3

THE ACTION OF INSULIN IN GLYCOGEN FORMATION AND ITS THERAPEUTIC APPLICATION¹

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THE theory that insulin is anabolic in its action, that it prepares and stores carbohydrate for burning but does not actually burn it, is the main thesis of this paper. The writer's attention was first drawn to this view by clinical observations, and particularly by the effect of exercise in increasing the hypoglycaemic action of insulin in diabetics under treatment. Some observations on this point and their immediate practical application have already been recorded (1), and in this paper further experiments with exercise on a diabetic are given and their significance with regard to insulin action is discussed. The literature bearing on the point is considered and leads to the conclusion that the main, if not the only, action of insulin is to form glycogen. Such a view may now be taken as definitely proved by the very recent communication of Best, Hoet, and Marks (2) to the Physiological Society, and the therapeutic applications discussed at the close of this paper are thus placed on an established physiological basis.

Some Exercise Experiments on a Diabetic and their Significance.

The effect of exercise on blood-sugar has been extensively studied. In normal individuals it is known to reduce the blood-sugar slightly, and in diabetics Allen (3) and others have clearly shown that it has invariably the same effect but to a greater degree, because the drop from an initial higher level is more obvious. In a recent article (1) it was shown that exercise greatly increased the hypoglycaemic effect of insulin and the practical importance of the fact in treatment was briefly discussed. Some further exercise experiments are recorded below and their significance in relation to the mode of insulin action is discussed.

The experiments are detailed in Tables I and II. They were carried out on a young diabetic man whom insulin has restored to normal muscularity and who has had much experience in such experiments and the dietetic accuracy

¹ Received May 19, 1926.

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necessary for proper control. His usual carbohydrate diet is 20 grm. for breakfast and dinner and $7\frac{1}{2}$ for lunch, and his usual insulin 10 units in the morning and 8 in the evening. Insulin was omitted on the morning of the experiments and the blood-sugar allowed to be high in consequence at the starting-point of the experiments. $1\frac{1}{2}$ hours after lunch, at 2 p.m., 10 units of insulin were given. Probably 1 or 2 grm. of the lunch carbohydrate were still being absorbed during the first hour of the experiment. The exercise in experiments A and C, on a heavily braked fixed bicycle and rowing machine, was very strenuous and continuous from 2 to 4.30 p.m., except for a few minutes' interval for bleeding. It is interesting to note that muscular efficiency seemed quite as good without insulin as with it, nor did exercise make any appreciable difference to the amount of ketone bodies excreted, as judged by the nitro-prusside test in the urine, although more was present in experiments C and D when insulin was not given. A moderate glycosuria of from 2 to 4 per cent. was present whenever the blood-sugar was above 200 mg. per cent.

TABLE I.

Time.		A.		B.		C.		D.		E.
		Insulin.		Insulin.		Exercise.		No Exercise.		
		Exercise.		No Exercise.		No Insulin.		No Insulin.		
	Mins.									130 12.30 p.m.
2.0 p.m.	0	240	3	254	5	243	6	237	1	150 1.30 "
		Ins. 10 units		Ins. 10 units						
	20	245	15							
2.30 p.m.	30	—	—	242	+4	258	10			162 2.30 "
	45	219	—	—	—					
3.0 p.m.	60	175	15	239	8	268	7	222	+2	
	90	116	4	230	5	267	14			186 3.30 "
	120	73*	3	211	10	270	18	218	2	
4.30 p.m.	150	51*	2	181	2	268	19			

TABLE II. *Aftermath.*

Time.	A.	B.	C.	D.	F.
4.30 p.m.	51*	181	268	218	223 7.0 a.m.
6.15 "	20 grm. glucose	—	5 units	5 units	5 units
	*10 grm. sugar	120			
7.0 "	No insulin	8 units	—	8 units	150 9.30 a.m.
7.30 "	20 grm. C.	20 C.	*10 grm. C.	20 C.	
11.0 "	—	—	8 units. 20 C.	*	
8.0 a.m.	10 units				
11.30 a.m.	20 grm. C.				

* Symptoms of hypoglycaemia.

Blood-sugar figures in milligrammes per cent. The figures on the right of the columns of Table I are the arteriovenous differences. The onset of hypoglycaemic symptoms is taken as indicating a blood-sugar of about 70 mg. per cent. for reasons given in the text, in which further description of the tables is given.

Arteriovenous difference. Attention has been drawn in another paper (4) to the fact that the difference between the blood-sugar concentration in the arteries and veins can be looked upon as an index of the power of the muscles

or tissues to burn or store glucose. This difference, which may be as much as 50 to 90 mg. in the normal, is absent or slight in the diabetic, but is brought nearly to the normal by the use of insulin. This has been confirmed in experiments on depancreatized dogs. In the following experiments this difference has been ascertained by simultaneous estimations of capillary (fortunately the same as arterial) blood and of blood from the basilic veins. In the tables the capillary blood-sugars are given as milligrams in 100 c.c. of blood, and on the right of the same columns the difference is also stated, the venous blood-sugar being lower in every case except where a plus is put before the difference. The differences are often small, but as the duplicate estimations were very satisfactory, they have an undoubted significance.

Description of the Experiments.

The four experiments A-D are recorded in the order in which they were performed at two or three days' interval from each other, to allow the carbohydrate metabolism to come back to the patient's normal in the interval. It was not practicable to follow the blood-sugars in great detail for more than a few hours, and the period of close observation was set by the first experiment, A, in which moderately severe symptoms of hypoglycaemia occurred at the end of $2\frac{1}{2}$ hours, necessitating the administration of glucose by mouth for their relief. Along with each experiment, what I have termed the aftermath must be considered to obtain their full significance. No blood-sugar estimations were carried out during the aftermath. But it has been frequently established on this patient that the symptoms of hypoglycaemia always set in when the blood-sugar falls to about 70 mg. per cent., and that is taken to be the level of the blood-sugar in these experiments when symptoms of shakiness, palpitation, and lassitude occurred.

Experiment B may be considered first as a basis of comparison, as it represents most closely the patient's usual balance of diet and insulin, although the blood-sugar is abnormally high from the omission of the morning insulin. The blood-sugar fell slowly in the first $2\frac{1}{2}$ hours to the figure of 181 mg., and from numerous other curves done on the same patient would have been about 120 mg. at 7 p.m., when the usual evening 8 units were given with 20 gm. carbohydrate. Neither that evening nor next morning was there any sign of hypoglycaemia or glycosuria to indicate that the usual balance of diet and insulin was upset. The arteriovenous difference does not show any great change in this experiment from the effect of insulin, although some higher figures are obtained when insulin action becomes fully established.

Experiment A with exercise shows a striking difference. At the end of $2\frac{1}{2}$ hours the blood-sugar fell to 51 mg. per cent. and 20 gm. of glucose were given to relieve the hypoglycaemia—it had an appreciable effect within five minutes of administration. Twenty gm. of glucose is the usual amount that

balances 10 units of insulin in this patient. In spite of this, symptoms of hypoglycaemia recurred at 6.15 p.m., when 10 gm. of sugar were taken. The usual insulin was omitted before the evening meal (20 gm. C). But in spite of this extra 50 gm. of carbohydrate without insulin, the usual balance of diet and insulin was upset even next day and symptoms of hypoglycaemia occurred three hours after breakfast.

Experiment C gave unexpected results in that the blood-sugar rose as the result of exercise. Now, careful exercise experiments on diabetics by Allen and others have invariably shown that the blood-sugar falls during exercise, and this is undoubtedly so. It occurred in all grades of diabetics and was taken to show that the muscles of a diabetic could still utilize sugar to some extent. The different result in experiment C is explained by the fact that this patient had been having insulin, while the other cases formerly investigated had not. Insulin builds up a glycogen store (see later), and this is always liberated again as glucose in a severe diabetic when the effect of the exogenous insulin wears off. That glucose was being burned in this experiment is shown by the fact that the arteriovenous difference became greater the longer the experiment lasted, but it was outpaced by glycogenolysis and the blood-sugar rose. It would seem likely that an increased output of adrenalin may be partially responsible for this degree of glycogenolysis, for the exercise was certainly very violent. A similar rise of blood-sugar has been described in one or two cases of boxing experiments in normal individuals, although a fall was much more common. Hale-White and Payne (5) have found a similar rise in blood-sugar after exercise in a normal individual, which suggests that the explanation of the rise in experiment C is correct. After vigorous walking, the fasting blood-sugar was found to be 144 mg. instead of the usual 120, and when 50 gm. of glucose were given, a gradual fall to 95 mg. took place instead of the usual rise. Evidently glycogenolysis took place during the exercise, and, as is suggested later, when the glycogen stores are partially depleted, glucose is more readily stored away and the usual rise in blood-sugar is prevented. From the rate of the heart and the average arteriovenous difference observed in experiment C, and from the figures given for the output of the human heart, it can be calculated that at least 80 gm. of glucose were burned during these 2½ hours, and since the blood-sugar did not fall, the glucose must have been supplied from stores of glycogen. It would have been interesting to deprive this patient of insulin for two or three days, allow his glycogen store to become exhausted, and then to see if his blood-sugar fell after exercise. But this severe and somewhat dangerous experiment was impossible and might have made this a posthumous paper.

The aftermath of experiment C is also very significant. Five units of insulin were given at 4.30 p.m., as it was felt it would be better for the patient not to be left too long at that high blood-sugar level. Two and a half hours later, just before 7 p.m., symptoms of hypoglycaemia occurred. This was relieved by 10 gm. sugar, and then the usual evening dose of insulin and dinner carbo-

hydrate was taken without any resulting hypoglycaemia later in the evening. Nor was there any occurrence of hypoglycaemia next morning as in experiment A, so that it seems certain that far more glucose was burned and the carbohydrate stores far more depleted in experiment A than in C.

Experiment F is a contrast to the aftermath of C and shows how much smaller is the drop in blood-sugar when the glycogen stores are full. The figure 223 mg. is the fasting blood-sugar at 7 a.m. after the usual dose of insulin the evening before. An attempt had been made to raise this fasting level to a figure near the 268 mg. at the end of experiment C, but although 30 gm. extra carbohydrate were taken the evening before, the fasting level was only 223 mg. Two and a half hours after 5 units the blood-sugar had only fallen to 150 mg., although it started at a much lower level.

Experiment D, without exercise or insulin, shows the gradual fall in blood-sugar that occurs when the relative hyperglycaemia from the carbohydrate of the lunch is wearing off from the combined effect of a moderately heavy glycosuria and the action of the patient's own meagre supply of insulin. It is to be presumed that, as insulin had already been withheld for nineteen hours, much of the stored glycogen had already escaped and the blood-sugar had settled to a nearly constant level. Experiment E is a contrast to this and shows the rise in blood-sugar that occurs when insulin is just beginning to wear off. Here the usual dose of insulin had been given at 8 a.m., the lowest figure (higher than his usual at this time) was found at 12.30 p.m., after which the blood-sugar steadily rose as glucose reappeared from the stored glycogen. The results in experiments D and E have been confirmed at other times and will be familiar to clinical workers with insulin. It should also be noted in D that the absence of an arteriovenous difference shows that the muscles were neither burning nor abstracting glucose from the blood. In contrast to the aftermath of B, where no hypoglycaemia occurred, mild symptoms were felt in the evening after D, probably because more glucose escaped in the urine during the afternoon of the latter experiment and the carbohydrate stores were more depleted.

Discussion of Experiments and Conclusions therefrom.

Although it was not possible to make these experiments complete by estimating the amount of work done, the calories expended, and the respiratory quotient, yet some important conclusions regarding insulin can be drawn from them.

1. The immediate effect of exercise in increasing the hypoglycaemic action of insulin is clear from a comparison of experiments A and B and requires no further discussion.

2. Exercise burns up carbohydrate and empties the glycogen stores in a way that insulin alone cannot do. In experiment C, from the evidence that severe muscular work was efficiently performed and that the arteriovenous difference became greater, it seems that, for a time at any rate, exercise can burn carbo-

hydrate without the help of actively circulating insulin. The great effect of 5 units after this exercise in experiment C is taken as further evidence that glycogen stores had been used up (see next paragraph). But the combined effect of insulin and exercise is greater in burning carbohydrate than that of exercise alone, because on the day succeeding experiment A the usual balance of diet and insulin was still upset, in spite of the omission of one dose of insulin and the addition of 50 gm. extra carbohydrate to the diet. The fact that exercise not only increases the immediate hypoglycaemia of insulin but also burns up and empties glycogen stores is further supported by some observations (1) which showed how exercise reduced the fasting blood-sugar next day in a diabetic.

3. When glycogen stores are empty, insulin is much more effective in its hypoglycaemic action than at any other time. This is shown by the comparison of the great effect of 5 units after experiment C with the smaller effect in F. Still more striking is the fact that 5 units during a rest period after C had the same hypoglycaemic action as 10 units with exercise in experiment A. Glycogenolysis and depletion of the body of carbohydrate must have been extreme during C, because, although as much work was performed and as much carbohydrate presumably burned as in A, the blood-sugar rose and a heavy glycosuria was present all the time.

Some writers have described a condition which they call a 'glucose vacuum', in which a diabetic is able to tolerate far more glucose without hyperglycaemia after a short period of starvation than before. From the above experiments there would appear to be a *glycogen vacuum* also which insulin very rapidly fills from circulating glucose. The more complete the glycogen vacuum, the greater the hypoglycaemic action of insulin. The glycogen-holding capacity of the normal individual is certainly far greater than the glucose one, probably by 300 or 400 gm. of glycogen to 70 or 80 gm. of glucose. It would, therefore, seem likely that a 'glycogen vacuum' is a much more important factor in connexion with the phenomenon described as a 'glucose vacuum' than the mere content of glucose in the body. At any rate it was not an absence of glucose at the end of experiment C (blood-sugar = 268 mg. per cent.) that made insulin action so very effective, but almost certainly the depletion of the glycogen stores.

Clinically the same marked action of small doses of insulin can be seen when glycogen stores are low, although the blood-sugar is high. Small doses of insulin have a great effect at the beginning of the treatment of severe emaciated diabetics, but a much smaller effect later, as is shown rather clearly in the following case :

A severe diabetic had been treated with a constant diet of 36 gm. carbohydrate, 75 protein, and 110 fat for some weeks. He excreted about 10 gm. of glucose a day and his fasting blood-sugar was always about 180 mg. per cent. He received 10 units of insulin as his first dose and the blood-sugar fell from 182 mg. to 107 at the end of $1\frac{1}{2}$ hours and to 78 after 6 hours. Next morning his fasting level was 83 mg., and for the next few days a dose of 5 units once

a day kept his blood-sugar normal. In the next few weeks more and more insulin had to be given to keep his blood-sugar near normal limits, and during this period he broke diet on two occasions. At the end of four weeks he was receiving 25 and 15 units, morning and evening, on the above constant diet. His weight had increased by this time and he was feeling much stronger. One morning his fasting level was 177 mg. per cent.; he was given 25 units, his breakfast was withheld, and he was kept under close observation. One and a half hours later his blood-sugar had only fallen to 146 mg., which was far less than the effect of 10 units on the first day of treatment, even when carbohydrate had been given for breakfast.

The increased tolerance for insulin in these cases seems to be entirely due to the increased glycogen store which insulin builds up. It has been observed in many cases and recorded by other workers on insulin. It is one of the reasons for avoiding the initial treatment of cases by starvation or severe carbohydrate privation. For when we start with a very depleted carbohydrate store, it fills very slowly, and instead of perhaps a fortnight, it takes four, six weeks, or more to get the correct balance between the diet, the glycogen stores, and the insulin dosage. I am indebted to Dr. G. A. Harrison for the records of the beginning of this case and for pointing out initially the importance of considering the probable condition of the glycogen stores in treatment.

The above evidence all suggests that the main action of insulin is to change glucose into glycogen, but not actually to burn it. When it has performed this function, it has changed the glucose into a utilizable form, and the actual burning takes place under the stimulus of the central nervous system to muscular activity. We shall see in the next section how the sum total of the experimental work on insulin supports this view.

Experimental Evidence of the Mode of Insulin Action.

Among the hundreds of papers that have appeared on insulin action, the clearest fact that emerges is that insulin reduces blood-sugar. It is agreed that this action does not take place in isolated blood, but only in blood circulating through various tissues *in vivo*. This depletion of blood-sugar might be caused by the actual burning of glucose in the tissues or by the change of glucose into some other form of carbohydrate. The first would be shown by an increase in the total oxidation and metabolism of the body, and the second by changes in the store of glycogen or other form of body carbohydrate besides glucose. We must therefore seek for evidence as to whether insulin primarily burns or stores glucose, and for this purpose we must examine the effect of insulin on both normal and diabetic metabolism.

Insulin does not increase Metabolism.

From the exhaustive review of Campbell and MacLeod (6) on the effect of insulin on *normal animals*, it is clear that there is no increase of metabolism or oxygen consumption until the blood-sugar falls to a hypoglycaemic level and produces increased muscular tone and tremors. When the onset of this increased

muscular tone is prevented by curare, Krogh found that the oxygen intake usually decreased slightly. In normal human beings Kellaway and Hughes (7) showed that the amount of sugar disappearing from the blood under insulin action could be accounted for neither by a corresponding rise in oxygen consumption, nor CO_2 or calorific production. Since then this has been repeatedly confirmed on normal animals, and most observers (8) have failed to find a rise of metabolism as the result of insulin injections until the onset of tremors or convulsions which have increased the oxygen consumption, &c., by the muscular activity involved in that condition. Indeed, until the onset of this increased muscular activity, many observers have found the metabolism and the temperature to be slightly lowered. Certainly in some cases insulin raised the R. Q. independent of increased muscular tone, but this it seems to do by shifting all the oxidation to the carbohydrate side, probably by making enough carbohydrate available for burning to prevent the use of protein and fat.

In *diabetics*, on the other hand, insulin has been definitely shown to increase the oxygen consumption and metabolism as well as to raise the R. Q. But this does not prove that insulin is the stimulating agent in causing the burning of glucose, but merely that it supplies the necessary oxidative substrate, a link in the chain necessary for oxidation of carbohydrate, to enable the hitherto defective metabolism to be brought up to normal. The significant fact in the question whether insulin burns carbohydrate is not the increase of oxidation and metabolism that it causes in the diabetic, but the failure to produce this increase in the normal.

There is no evidence, then, that insulin directly increases the combustion of carbohydrate. It would indeed be wasteful and unphysiological if it did so. The normal stimulus to insulin production is the raised blood-sugar arising from ingested carbohydrate, and the function of insulin is to store this glucose away until required for oxidation.

Insulin forms Glycogen from Glucose.

The evidence of the power of insulin to form and store glycogen is clear and unequivocal. The liver and muscles of a diabetic animal are markedly deficient in glycogen, and the workers of the Toronto school (Banting and Best) showed very early that insulin builds up a store of glycogen in the muscles and especially in the liver of a depancreatized dog. In normal animals it was found that large doses of insulin reduced the amount of glycogen, and for a long time it remained a puzzle how insulin could at one time build up a glycogen store in the diabetic and at another diminish it in normal animals. But it has since been shown by Heymans (9) and others that at the beginning of hypoglycaemia insulin does not reduce the glycogen store of the liver, and that this only occurs on death from prolonged hypoglycaemia accompanied by convulsions. We know that in the latter condition two new factors come into play. Firstly, the increased muscular action during the convulsions itself burns up

some of the glycogen; and secondly, there is an increased output of adrenalin which causes a protective glycogenolysis in the hypoglycaemic condition and raises the blood-sugar at the expense of the muscle and liver glycogen. It would seem, therefore, that the paradox that insulin can reduce glycogen stores in a hypoglycaemic animal is to be explained not by a direct effect of insulin, but by a secondary adrenalin mechanism which the hypoglycaemia evokes.

A recent communication of Best, Hoet, and Marks (2) to the Physiological Society proves conclusively that insulin changes circulating glucose into stored glycogen in the muscles. By experiments in which they perfused an eviscerated skin muscle preparation of a cat with glucose and insulin, they found that the glucose was changed almost quantitatively into glycogen in the muscles.

Summary of Insulin Action.

In a normal individual, the rise of blood-sugar from ingested carbohydrate calls forth an increased production of insulin. This stores the excess glucose as glycogen³ in the muscles and liver until it is required for oxidation. When an excess of insulin is administered to a normal, it does not increase the tissue oxidation, because insulin is merely concerned with preparing the oxidative substrate. When the excess of insulin has reduced the blood-sugar to a certain hypoglycaemic level, a sympathetic adrenalin reaction comes into play, causes glycogenolysis, and raises the circulating glucose, or at least prevents it falling lower, unless the dose of insulin is very large. In the diabetic an injection of insulin increases the oxidative substrate glycogen; the metabolism can now rise to the normal and combustion is increased above the former diabetic level. If the substrate is not wanted for immediate use, a glycogen store is formed, but cannot be maintained long after insulin is withdrawn. If the diabetic is requiring much carbohydrate for immediate use, as in the exercise experiments in the beginning of this paper, the substrate is rapidly used up and the blood-sugar is reduced to a far greater extent than in a condition of rest. Moreover, if the glycogen stores are empty, as in the aftermath of experiment C, or at the beginning of insulin treatment in severe starved diabetics, insulin is unusually effective in lowering the blood-sugar, presumably by turning it rapidly into the glycogen vacuum.

The Relation of Fat and Carbohydrate Metabolism.

It is suggested, then, that the function of insulin is to change glucose into glycogen, thereby storing it and preparing it for burning. In performing this function insulin has to deal with more than the mere glucose derived directly from ingested carbohydrate. It is certain that protein eventually produces in the body half its weight of glucose from deaminized amino-acids. That this glucose also requires insulin for its normal metabolism is usually taken for

³ The part played by lactacidogen (10 and 11) as a probable intermediate stage between glucose and glycogen does not essentially affect, and need not enter into, this discussion.

granted, and is abundantly proved by the increased insulin that a diabetic requires when protein is added to a diet otherwise constant in the other food-stuffs and in total calories. Further, no theory of insulin action is complete that does not take into account the relation of fat to carbohydrate metabolism and the possible conversion of one substance into the other. It is certain that carbohydrate is changed into fat in the body and stored as such from the evidence of fattening animals on pure carbohydrate diet, but it is not yet conclusively proved that fat is changed into carbohydrate. Diabetic metabolism gives evidence that can hardly be gainsaid on this point, and evidence from other sources also is very strong. The question is of such importance in considering the insulin regulation of carbohydrate metabolism and the insulin requirements of the diabetic, that I shall enter in some detail into the clinical and experimental evidence in favour of a direct conversion of fat into carbohydrate, probably in the liver.

Evidence that Fat is transformed into Carbohydrate.

Although most attention has been paid to carbohydrate abnormalities in diabetes, the disturbance in fat metabolism is almost equally striking and well recognized. An increased lipaemia is an invariable accompaniment of severe untreated diabetes and usually runs parallel with the severity of the disease. Insulin reduces the hyperlipaemia at the same time as the hyperglycaemia. The Toronto school of workers early showed the same state of affairs in depancreatized dogs which were fed on sucrose. The livers of these dogs contained an abnormally high percentage of fat and a very low glycogen content. Injections of insulin along with the sucrose completely reversed the fat glycogen content, reducing the former to normal and increasing the latter to the very high figure of 20 per cent. in one dog and 7 and 12 per cent. in others. This does not prove that insulin converts fat into glycogen, but does suggest that it is essential to the normal balance of fat and glycogen in the liver.

Further strong evidence that fat is converted into carbohydrate is afforded by the effects observed in feeding diabetics with fat. The work of Allen, Sherrill, Joslin, and others has shown that when fat is added to the diet of a diabetic whose diet and insulin (whether endogenous or exogenous) has been so balanced as to maintain a normal metabolism, hyperglycaemia and eventually a heavy glycosuria supervene. This has invariably occurred in my clinical experience. The most reasonable explanation is the direct conversion of the excess of fat into glucose which produces hyperglycaemia in the absence of sufficient insulin to convert it all into glycogen. This hyperglycaemia caused by fat feeding is much more resistant to insulin than a temporary hyperglycaemia caused by an excess of ingested carbohydrate, probably because blood-sugar is being continually liberated from fat, whereas the hyperglycaemia of excessive carbohydrate ingestion reaches an acme which is soon reduced by insulin and by the loss as glycosuria when all the carbohydrate is absorbed.

A similar hyperglycaemia caused by high fat feeding has been observed in

normals. Recently, Weeks and others (12), working on the effect of different diets on epilepsy, brought a pertinent fact to light. They found that the only diet which caused hyperglycaemia in these epileptics was a high fat diet. This seems somewhat paradoxical, but is easily explained. The carbohydrate of the diet was low, and hence the normal stimulus to insulin production was absent or slight. The fat was being changed into glucose, but insufficient insulin was present to store this glucose as glycogen, and hyperglycaemia was produced. Allen (13) has produced a similar hyperglycaemia in normal puppies by high fat feeding.

The conversion of fat into carbohydrate is supported by other general physiological considerations. It is not certain what percentage of our total metabolism, both active and resting, is produced in muscular activity, but when all the activity of our striped and unstriped muscle is taken into account, it probably leaves very little to general tissue oxidations. Now there is no other substance than carbohydrate known to be burned in muscular contraction, and it would seem that our processes of metabolism are overwhelmingly muscular. It is quite clear, too, that stores of body fat are used up, and very quickly too, in severe exercise, and this must involve the conversion of fat into carbohydrate. Krogh and Lindhard (14) showed in 1920, from their studies of its respiratory quotient, that muscular contraction involved the burning of nothing but carbohydrate, and Furusawa (15) has recently confirmed this. He showed that even on high fat diets the initial R. Q. of exercise is unity, but that it fell more rapidly than in carbohydrate-fed animals, because the initial store of carbohydrate of the resting muscle was smaller on fat diets, and, when the initial store was burned, it had to be replenished sooner from stores of fat, involving a lowered R. Q. Hetzel and Long (16) have shown the same condition in diabetics. When insulin has been recently available, the initial R. Q. of exercise is unity and all the processes of lactic acid formation and removal are the same as in a normal individual. But the R. Q. falls more rapidly than in the normal. 'In this respect the diabetic individual, with recent insulin on a diet poor in carbohydrate, behaves in a manner exactly similar to a normal man on a diet consisting mainly of fat.' When insulin has been long withheld in the diabetic, exercise raises the R. Q. much less, even for short periods of exercise, and it rapidly falls to its original low level because the store of oxidizable carbohydrate substrate in the muscles, presumably glycogen, is very defective in the absence of insulin. Working with the D/N ratio in phloridzinized animals Hartogh and Schumm (17) obtained ratios which can be explained only by the direct transformation of fat into carbohydrate, and Burn and Marks have recently placed this beyond all doubt in experiments with the perfused liver of cats (personal communication, at present in the press).

From the above evidence it seems certain that fat can be converted into glucose without insulin, but that, in the absence of insulin, it accumulates as glucose and is not changed into glycogen. Glucose produced endogenously would therefore appear to be less stimulating to insulin production than ingested

carbohydrate. Although it is probable that the conversion of fat is going on all the time, it seems likely that it is especially active when combustible carbohydrate, i.e. glycogen, is insufficient to meet the metabolic requirements. A hyperlipaemia and an increased mobilization of fats occur most markedly in two conditions in which glycogen is deficient: in diabetes, where combustible carbohydrate is lacking in spite of the high blood-sugar, because insulin is defective; in starvation in normal individuals, where increased lipaemia sets in after some thirty hours, when it can be computed that the glycogen stores are exhausted. The essential stimulus, then, to increased conversion of fat into glucose would seem to be an insufficiency of glycogen, available carbohydrate, to meet the calorific requirements. Although it is not possible to enter fully into the question of ketosis here, it is interesting to note that it sets in at the same time as the glycogen store becomes insufficient and the mobilization of fat begins, both in normals and in diabetics. It is usually stated that ketosis occurs from imperfect oxidation of fats in the absence of actively burning carbohydrate. It seems to me more probable that the production of ketones may not be such an abnormal step in metabolism, but is a usual step in the conversion of fat into carbohydrate. Clutterbuck and Raper (18) have just published some *in vitro* experiments suggesting a possible mode of such a conversion. In normal conditions of diet and metabolism this conversion goes on gradually and there is no undue accumulation of ketone bodies. When combustible carbohydrate is deficient, as in starvation and in diabetes, the conversion of fat is greatly augmented and clinical ketosis appears. When insulin abolishes or reduces ketosis in diabetes, as it undoubtedly does, it acts not necessarily by correcting the imperfect oxidation of fats, but it supplies enough glycogen to meet the momentary calorific requirements of metabolism, and the excessive conversion of fat into glucose with the accompanying production of ketone bodies is stopped. In a diabetic doses of insulin which will lower the blood-sugar to a hypoglycaemic level will not abolish ketosis so effectively as when plenty of carbohydrate and insulin is available and the blood-sugars are higher. The whole question is by no means clear, but in the meantime it is suggested that clinical ketosis involves no really abnormal paths of metabolism, but is an accompaniment of an augmented conversion of fat into carbohydrate, when insufficient glycogen is present to meet the energy requirements either in conditions of carbohydrate starvation in normals or of insulin deficiency in diabetics.

This theory rather complicates than simplifies matters, for it postulates some further hormone or stimulus to increased conversion of fat to carbohydrate when glycogen is deficient. There is some evidence to make us turn to the pituitary in this connexion. Coope (19) has shown that injections of pituitrin cause an infiltration of the liver with fat, and insulin stops this. Pituitrin also antagonizes insulin by causing glycogenolysis in the liver. The adiposity of conditions of pituitary deficiency and the hyperglycaemias of hyperpituitarism undoubtedly have some bearing on the point.

Summary.

The evidence that fat is directly changed into carbohydrate is reviewed and the relation of this conversion to insulin action and insulin requirements is considered. It is suggested that this conversion is always going on, but is greatly augmented when glycogen is not available for body requirements. Fat can be converted into glucose without insulin, but causes a hyperglycaemia in the absence of insulin. Ketosis accompanies this conversion and insulin checks ketosis by producing sufficient glycogen, i. e. combustible carbohydrate, to meet oxidative requirements, thus stopping the conversion of fat into carbohydrate.

The Insulin Regulation of Total Metabolism and its Practical Application.

Before the introduction of insulin Allen had become convinced of the importance of the total regulation of the diet in the treatment of diabetes and had demonstrated the harmful effect of increasing any form of food-stuff beyond the calorific requirements. All careful subsequent workers have agreed with him. As a result of detailed studies of the insulin requirement of the organism, Allen (20) came to the following conclusions:

'1. The insulin requirement of the organism is governed not only by carbohydrate but also by fat and all other elements entering into the diet and metabolism.

'2. It remains uncertain whether insulin is directly concerned in total metabolism, or whether it is specifically related to the assimilation of glucose alone, and only in some secondary or indirect manner with the metabolism of other foods. It can only be said that the body cells somehow require insulin for their nutrition and consume it at rather a rapid rate in the life processes. Its anabolic is probably as important as its catabolic function.'

From the arguments in this paper it is suggested that the function of insulin is purely anabolic, and that it is catabolic only indirectly in so far as it prepares the oxidative substrate glycogen which can be used as the body activities need it. The insulin requirement of the body is governed by the total amount of glucose produced from exogenous or endogenous sources, and the function of insulin is to turn this glucose into glycogen. Insulin requirements therefore depend on the sum total of the metabolism of all three food-stuffs, because it has to deal with glucose derived directly from ingested carbohydrate, and indirectly from protein and from fat.

Therapeutic Application.

This hypothesis of insulin action, both endogenous and exogenous, fits in exactly with the facts observed in the treatment of diabetes and helps us to understand what we can achieve with insulin and what we cannot hope to do.

All except very severe cases of diabetes can be made sugar-free with normal

blood-sugars by starvation and severe under-nutrition. Although their metabolism may be normal from the diabetic point of view, i.e. an absence of hyperglycaemia and often of ketosis, it is one of starvation, which will eventually lead to death. They remain sugar-free because their endogenous insulin is sufficient to change the small amount of glucose produced from their diet or body-stores into glycogen, which is rapidly catabolized, and the sugar never accumulates. But insulin must be given to such cases to enable them to utilize a diet sufficient to support life. When in such a case the diet is raised considerably, but still kept at a level under their full metabolic requirements, it is found that very little insulin is required to keep their blood-sugars normal throughout the twenty-four hours. They may not lose further weight, but they are lacking in energy and muscular strength, and their metabolism is obviously one of undernutrition. Their insulin prepares enough oxidative substrate for them to live on, but they use it all up and store none. When the insulin action wears off, the blood-sugar still remains normal because there is no glycogen to come out of store. This is the condition in which adrenalin and pituitrin fail to relieve insulin hypoglycaemia (21), because glycogenolysis cannot occur from the empty stores. When the diet of such a case is raised even a little above the actual calorific requirements, a very different condition of metabolism is established, quickly if the addition be carbohydrate, slowly but equally surely if it be protein or fat. The blood-sugar, instead of maintaining a steady normal level, begins to oscillate, and much larger doses of insulin have to be given if it is to be kept anything like normal during part of the day. If insulin is given in two doses a day, and it is hardly ever practicable to give it oftener, in doses which will reduce the blood-sugar almost to the hypoglycaemic level, it is always found in severe cases that when insulin wears off the blood-sugar rises again, often sufficiently to cause traces of glycosuria in the early morning. The excess of carbohydrate over the calorific requirements has been temporarily stored, not burned, and reappears as glucose when the effect of the exogenous insulin wears off. This recurrent hyperglycaemia cannot be prevented by large doses of insulin, unless they are given perhaps every five or six hours. But it can be prevented or greatly reduced by exercise which burns up the glycogen which insulin has prepared. The metabolism of such patients is alternating between the normal, when under the influence of insulin, and the diabetic, when insulin wears off. But they feel well and full of energy and are liable neither to the symptoms nor complications of the disease, if their hyperglycaemia is controlled daily as far as possible and not allowed to become continuous. They do not suffer from the lassitude and hunger that invariably seem to accompany the undernutrition diets that are necessary to maintain constantly normal blood-sugars in severe cases. A carbohydrate store is a physiological necessity, and it would appear that a diabetic cannot be active and comfortable without at least a small one. The ideal is to make the store as small as possible by making the diet intake exceed the calorific output as little as possible. But as the activities of the patient are bound to vary from day to day, the margin cannot be made

too fine, and constantly normal blood-sugars must be sacrificed to well-being and muscular efficiency. I find, and my patients do too, if they perform urine tests, that it is impossible to keep this margin constant, and that their diet and insulin occasionally require readjustments to avoid either hypo- or hyper-glycaemia (22). The position of less severe cases is quite different, because, with a sufficient diet, they have enough endogenous insulin to maintain a glycogen store and normal blood-sugars throughout the twenty-four hours. Small doses of insulin only are given to balance the immediate hyperglycaemic effect of the carbohydrate of the meals. These are the cases whose endogenous insulin (carbohydrate tolerance) improves most and who are often able to give up their insulin after a time. On the other hand, after the initial improvement at the commencement of treatment, the severest cases tend to improve very little if at all, because it is practically impossible to keep their blood-sugars at a level which will allow the pancreas to rest and regenerate, presumably below 0.12 per cent., if we accept Allen's hypothesis. In severe cases a fluctuating blood-sugar seems essential to activity and well-being, but inimical to possible recovery. There is never any doubt which the patient prefers.

These different conditions of metabolism, blood-sugars, and insulin requirements were carefully observed by Dr. Harrison and myself in 1923 over long periods on three patients. We had to give up as impossible the attempt to improve these patients permanently by keeping their blood-sugar constantly normal, or, if not quite impossible, as being too exacting on the patients without bringing them adequate benefit.

Level of the Fasting Blood-sugar.

A great deal of discussion has centred around the *ideal* level of the blood-sugar in insulin cases, and particularly the fasting blood-sugar, but very little of the *practicable* level. Most are agreed that the fasting level should be, if possible, within normal range (0.08 to 0.12 per cent.), and many authors seem to suggest that this is easy of achievement. I must confess failure in severe cases in this respect, and have rarely been able to keep a normal level except on occasional days on an adequate, though not a high, diet.

I agree that a normal fasting level is fairly easily maintained in less severe cases on an adequate diet; and in severe cases on an under-nutrition diet even with small doses of insulin, or on an adequate diet with frequent doses of insulin. But an under-nutrition diet for long periods is bad treatment, and more than two doses a day are rarely practicable. So I felt the fasting level must be left to look after itself when the two following rules have been fulfilled.

The severe patient should be kept on the lowest diet that will maintain him at a moderate weight in sufficient health and energy for his normal life pursuits. The diet must of course be modified to the activities and to the individual variations in food requirement, some requiring only 25, others even 40 calories per kilogram of weight. Then, the highest dose of insulin that can

be tolerated without hypoglycaemia or intense hunger should be given before the morning and evening meals, which should be the heaviest of the day. Having done this we can hope for a normal fasting blood-sugar, but cannot always maintain one. I find that on diets which usually provide from 30 to 35 calories per kilogram of body-weight in adults and 30 to 50 gm. of carbohydrate, 30 units a day is rarely, and 45 units a day is never, exceeded, except temporarily in sepsis, coma, or severe ketosis.

Unfortunately, many severe cases feel definitely better when traces of sugar are present in the urine at some time of the day, usually after breakfast, and do not feel so well when the blood-sugar drops as low as 0.06 or 0.07 per cent. even although no actual symptoms of hypoglycaemia are present. One of the difficulties of treatment is to persuade patients that they should keep entirely sugar-free—as I believe they should for their ultimate welfare—though they feel better when their range of blood-sugar is from 0.18 to 0.1 per cent. than when it is from 0.14 to 0.07 per cent. In the latter condition they are often languid and perpetually hungry. For these reasons I seldom try to lower the blood-sugar of severe cases below 0.1 per cent., and am forced to allow the fasting level to be as high as 0.16 to 0.20 per cent. in some cases.

I believe, however, that normal blood-sugars, when possible, confer great benefits in increased security to the patient. These are the cases that do undoubtedly improve most in their carbohydrate tolerance. They are also free from the complications that hyperglycaemia may bring, eye and skin affections, &c., and are in a position of comparative safety when sepsis or intercurrent illness reduces the efficacy of insulin.

Treatment by High Diets and High Insulin.

Some writers (23, 24) advocate the use of high diets and high insulin dosage to strengthen the patient and incidentally to fatten him. Sansum and others (24) in a recent paper describe the treatment with diets of 200 gm. of carbohydrate and 100 to 150 units of insulin, and state that 'they have no difficulty in keeping patients sugar-free and with a normal blood-sugar'. There is no mention of the fasting blood-sugar level in their paper. Apart from the expense and inconvenience of such large injections, the view of insulin action advanced here makes such treatment seem quite unphysiological. Nothing is easier than to fatten a patient with much food and insulin, but this is only storing food as glycogen and fat which is not wanted for immediate metabolism, and which will reappear from store as glucose when insulin is withheld or reduced. The re-appearance of glucose and ketones from stored glycogen and fat would be a grave danger when toxæmias interfered with the usual action of insulin.

Importance of the Condition of the Glycogen Store.

As already mentioned, the probable condition of fullness or emptiness of the glycogen stores is of great importance in treatment. Failure to consider this

leads to many mistaken ideas of a patient's real condition. Improvement has been claimed after many forms of treatment because the glucose tolerance has apparently been increased, whereas the real explanation is often merely that the glycogen store has been reduced and temporarily absorbs more glucose, as a dry sponge might. After periods of starvation, the patient's permanent carbohydrate tolerance has often been over-estimated in this way, and the slightly excessive prescription of carbohydrate ultimately manifests itself in glycosuria, when the stores have been filled to overflowing. The patient, however, usually bears the brunt of the blame and is suspected of breaking diet when he relapses, perhaps several weeks later. Again, the glycogen store is empty at the beginning of treatment in very severe cases, although the blood-sugar may be high, and unexpectedly small doses of insulin may produce a severe hypoglycaemia. The raised insulin requirement of these cases later in treatment when they have built up a glycogen store is no evidence that their tolerance is any worse and need not be viewed with alarm.

Summary.

1. Some experiments on a diabetic are described, contrasting the effect of insulin on blood-sugar with and without exercise. They show that exercise greatly increases the hypoglycaemic effect of insulin and burns carbohydrate and depletes the glycogen stores in a way that insulin alone cannot do. When the glycogen stores are empty insulin is much more effective in reducing blood-sugar than at any other time. Arguments are adduced to show that insulin is anabolic, not catabolic, in its action, that it forms glycogen from glucose, but does not burn carbohydrate directly.

2. The experimental evidence in favour of this hypothesis of insulin action is reviewed.

3. Clinical and experimental evidence of the conversion of fat into carbohydrate is put forward and the connexion of insulin with the process is discussed. It is suggested that the production of ketones is an accompaniment of the normal conversion of fat into carbohydrate. This is accentuated and becomes obvious as clinical ketosis when oxidizable carbohydrate or glycogen is insufficient to meet the metabolic requirements, as in starvation and severe diabetes. Insulin abolishes diabetic ketosis by providing sufficient oxidizable carbohydrate for the immediate catabolic requirements, thus checking and making unnecessary the increased conversion of fat into carbohydrate with its resulting ketosis.

4. It is suggested that the insulin requirements of the body depend on the total metabolism of the three food-stuffs, because insulin has to change into glycogen the glucose derived from carbohydrate, protein, and fat, both exogenous and endogenous.

5. The therapeutic aspect of this glycogenic theory of insulin action is considered, particularly in connexion with the regulation of the blood-sugar level in diabetes. The impossibility of maintaining a normal fasting level in severe cases on adequate diets is pointed out.

AFTERNOTE.

Since this paper was completed, further evidence (2) has been brought to the writer's attention which makes it probable that insulin, besides its main action in glycogen formation, *checks the formation of new sugar from protein and possibly from fat*. This must be mentioned here because such an additional action does not contradict, but rather supplements the views and explanations put forward in this paper, and itself gains support from the phenomena recorded in these experiments. It is an additional explanation of the different blood-sugar pictures during exercise with and without insulin in experiments A and C, and its explanation of how insulin checks ketosis is almost identical with the view expressed in this paper. But, although proof is lacking, it is my strong impression from clinical observation that a sufficiency of glycogen rather than of mere insulin is what checks the production of ketosis (see p. 80). Whether there is a common factor unifying and controlling this apparently double action of insulin in forming glycogen and inhibiting the new production of sugar does not matter practically. Both are strongly anabolic in their action.

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SOME OBSERVATIONS ON THE RECORDED MORTALITY
FROM DIABETES IN RECENT YEARS IN ENGLAND
AND WALES AS A WHOLE AND ITS PRINCIPAL
DIVISIONS, INCLUDING LONDON, WITH SPECIAL
REFERENCE TO THE INTRODUCTION OF INSULIN¹

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Introduction.

THOUGH insulin was only discovered in the early part of 1922, such energetic steps were taken to promote in this country the manufacture of the substance in a genuine form that quantities of it, reliable in strength and action, were placed on the market early in April 1923, and within a few months thereafter the supply was sufficient to meet the home demand. Taking into account the estimated number of the diabetic population in this country and the average amount of insulin required for each diabetic person per week, to be referred to more fully hereafter, it would appear, from records in the possession of the Medical Research Council relating to the weekly issues of insulin by British firms from the middle of 1923 onwards, to which we have been kindly granted access, that the use of insulin was not rapidly taken up by diabetics in general, though the preparation became available for the treatment of persons under the National Insurance Act at the same time as for the general public.

Statistics of the mortality from diabetes have now become available for England and Wales as a whole, and its main divisions, county boroughs, urban districts, rural districts, and London for the two years 1923 and 1924, and have also been obtained for London for the year 1925 by summation of the weekly deaths. Though it is not possible at present to hazard any definite opinion as to what changes in the mortality from diabetes may be produced in the future after a wider experience of the use of insulin, it seems not inopportune to compare the mortality statistics for the disease that are available for the years 1923, 1924, and 1925 with the corresponding statistics for previous years, to ascertain to what extent the mortality from the disease has declined in the different areas, and what changes, if any, have become apparent in its age distribution since the remedy was introduced.

¹ Received June 24, 1926.

Changes in Mortality from Diabetes in England and Wales as a whole, and London, during the last 40 years.

Before passing to the comparison of the mortality from diabetes in the biennium 1923-24 with that in the immediately preceding two years, 1921-22, and the four-yearly period, 1911-14, it seems advisable to review briefly the diabetic mortality rates for England and Wales and London for the several decennial periods since 1881, to ascertain what variations have occurred therein during the last forty years. These death-rates are shown in Table I.

The points in this table that appear to merit special emphasis are:

(1) In males and females in the country as a whole, and in London, the diabetic mortality rate at all ages showed a tendency to increase from 1881 onwards till 1911-14, when a maximum was attained, after which a decline in mortality occurred.

(2) This increase in diabetic mortality from 1881 onwards was relatively greater in females than in males. In 1881-90 the mortality in females was only 60 per cent. of the male mortality, whereas in 1911-14 it was 86 per cent. In 1921-22 the rates were practically equivalent in the two sexes owing to the relatively greater fall in the male than in the female mortality-rate after 1911-14.

With reference to the first of these features, it cannot be stated with certainty that, had pre-existing conditions continued, there might not have been some increase in the mortality in one or other of the more recent years, as it is well known that periodic waves of mortality occur in many other diseases. Any such tendency, if present, however, might be obscured by the introduction in 1923 of the new factor in treatment that probably influences the mortality-rate. That, as indicated in the table, an appreciable decline in diabetic mortality in England and Wales in the different age-groups occurred, in males at least, before the beginning of 1923, or in the period when the use of insulin had not yet passed beyond the experimental stage, is confirmed by comparing the rate of mortality in the three years 1910-12 around the censal year 1911 with that in the three years 1920-22 around the censal year 1921. The populations at these times can be more fully relied upon than populations estimated for years more distant from the censal years. At all ages, ages 25-44, 45-64, and 65 upwards, the standardized death-rates from the disease in males in 1920-22 are only 84, 94, 75, and 81 per cent. of the corresponding death-rates in 1910-12.

Changes in Diabetic Mortality at Different Ages in England and Wales and its Main Subdivisions since 1911-14.

We now proceed to the more detailed analysis of the mortality from diabetes in recent years. The data on which this is based are given in Table II, and comprise the standardized death-rates² from the disease in the two sexes in the

² The term 'standardized' applied to the death-rates indicates that they have been reduced to a common standard and show the rates which would have obtained had the age constitution of the populations in question been similar to that of persons in England and Wales in 1901.

age-groups 25-44, 45-64, 65 and upwards, and at all ages, for England and Wales as a whole, and for its four subdivisions, London, the county boroughs, the urban districts, and the rural districts for the periods 1911-14, 1911-20, 1921-22, and 1923-24. These age-groups have been chosen for tabulation in preference to those at decennial intervals because they provide larger numbers. They correspond approximately with the three stages of life: before middle age, middle age, and old age. This is a quite convenient classification, as diabetes, using this term in its unrestricted sense, is well recognized to be usually more severe and more fatal in the first than in the last of these periods of life. With regard to the distribution of diabetic deaths at the different ages, it may be stated that of the total deaths from the disease in the country as a whole in the four years' period 1911-14 the percentages amongst persons in the age-groups 0-24, 25-44, 45-64, and 65 upwards were 7, 17, 42, and 34. For the forty years' period 1881-1920, the proportions in the different groups were practically the same, namely, 11, 20, 38, and 31 per cent. The age distribution of deaths in the two sexes showed no appreciable difference. As only 11 per cent. of the deaths from diabetes occurred at ages under 25, the standardized death-rates for this age-group have not been tabulated separately.

As our intention is to compare the mortality rates in certain age-groups in the biennium 1923-24 in England and Wales, and its principal divisions, with those in the corresponding data for previous years, the changes that have taken place can be made more clearly perceptible by taking the mortality-rate in each selected age-group in each division in the four-yearly period 1911-14, when a maximum mortality appears to have occurred, as a standard and by stating the corresponding death-rates in the later groups of years as percentages thereof. The death-rates in the decennium 1911-20 might have been taken as the criterion of comparison, but this period includes the War years 1915-18, and these rates are probably less reliable than those for 1911-14. The percentage ratios thus calculated are shown as integral numbers in Table III. The relative changes in diabetic mortality at the several ages that have occurred in the country generally and its four divisions in the period under consideration may be readily seen in detail by reference to this table; the principal features in each area will only be described briefly here.

England and Wales as a whole. In 1923-24 the death-rate in males at all ages has fallen to 77 per cent. of the corresponding rate in 1911-14; in the age-periods 25-44 and 45-64 a decline to 68 per cent. is shown. These reductions at all ages and at ages 45-64 are only slightly greater than those shown in the period 1921-22. In females the decline in diabetic mortality in 1923-24 amongst those in the different age-groups has been considerably less than in males. In 1923-24 the mortality-rate at all ages is still 92 per cent. of that in 1911-14. The death-rates at all ages and at ages 45-64 for 1923-24 are practically identical with the corresponding rates for 1921-22.

Rural districts. The decline in mortality amongst males at the different ages in 1923-24 is very similar to that in the country as a whole, the mortality-

rates at all ages, at ages 25-44, 45-64, and 65 and upwards in this period being 79, 69, 69, and 96 per cent. respectively of the corresponding rates in 1911-14. In females the decline in mortality at all ages and at ages 45-64 is slightly less than, but at ages 25-44 is identical with, that in males.

County boroughs. The decline in mortality in males in 1923-24 as compared with 1911-14 is again very similar to that in the country as a whole at all ages, at ages 45-64, and at ages above 65, but in the age-group 25-44 the decline is relatively greater. The rates of mortality at all ages and at ages 45-64 in 1923-24 are not, however, appreciably less than those shown in 1921-22. Amongst females at all ages there is practically no decline in diabetic mortality in 1923-24 as compared with 1911-14, but at the ages 25-44 and 45-64 a fall of 13 per cent. is shown.

Urban districts. The percentage reductions in diabetic mortality at the different ages in 1923-24 from the corresponding rates shown in 1911-14 do not differ appreciably from those for the county boroughs, unless at the age-groups 25-44 in males and 65 and upwards in females.

London. In 1923-24 the mortality rate in males at all ages has declined to 72 per cent. of that in 1911-14. At ages 25-44, 45-64, and 65 and upwards the rates are 75, 65, and 86 per cent. respectively of those in the earlier period. These mortality-rates in 1923-24 all remain practically at the same level as in the previous biennium. Amongst females the mortality at all ages in 1923-24 has only fallen to 84 per cent. of that in 1911-14, but at the ages 25-44 it has declined to a somewhat greater extent than in the males. In the age-period 45-64 the mortality-rate slightly exceeds the corresponding rate for 1921-22.

Statistics for the year 1925 have only been obtained for London. If, as is most probable, insulin has been used as a remedy more extensively in London than in other divisions of the country, its maximum effect on the diabetic death-rate should consequently be shown in this area. On this account it seems advisable to analyse the diabetic mortality in London in somewhat greater detail. The standardized death-rates from the disease in the two sexes and persons in similar age-groups to those already described for the individual years 1921-24 inclusive, and for persons only for the year 1925, and the mortality-rates for the years from 1922 to 1925 expressed as a percentage of those in the corresponding age-groups in 1921, are given in Table IV. This table shows that the diabetic mortality-rate in males at all ages in 1924 is almost identical with that in 1921, whereas that in females has fallen only 6 per cent. in the same interval. For persons, the death-rate at all ages in 1924 remains almost at the same level as in 1921, but falls to 87 per cent. of this rate in 1925. The relative changes in mortality in the several age periods may be seen in the table; the special features that seem to merit emphasis will be referred to later in the discussion.

Discussion.

Having compared the mortality statistics for diabetes in the separate sexes and persons at certain ages that are available for the country as a whole, and its

main divisions, including London, for the years 1923, 1924, and 1925 with the corresponding statistics for previous years, we shall now discuss the nature and extent of the changes that have become evident in these in the last three years and the factors to which they probably owe their origin.

Unfortunately, we have no accurate information regarding the number of cases of diabetes in this country. If it be assumed that cases of diabetes survive on the average only three years after the disease is diagnosed, a rough approximation to the number of the diabetic population in any year may be obtained by taking three times the number of deaths. Computed on this basis, the total number of diabetic cases existing in 1923 or 1924 would be about 13,000 in England and Wales. It is possible, however, that an average duration of three years is too low. Joslin (1924) has published for two periods of years, one before June 1914 and another from June 1914 to January 1918, for an extensive series of fatal cases of diabetes, the average duration of the disease in groups of cases originating in the different decades of life. He gives the average duration at all ages as 4.8 years in the earlier, and 6.0 years in the later period. For the complete series the mean duration is 5.6 years. If this average duration be considered to hold for England and Wales, the number of diabetic cases would be about 24,000, a number which is increased by fully 1,000 if calculated from the average durations in the several decades of life. The use of Joslin's averages thus provides an estimate which is roughly twice that based on the previous assumption. As such a difference exists between the two estimates, it is fortunate that an approximation to the number of the diabetic population can be obtained by the use of factors from another source, though it is doubtful to what extent they may be considered applicable to the present data. In 1910 there were published in Berlin the results of an extensive investigation into the relationship between sickness and mortality amongst insured persons in Leipzig and its neighbourhood³ based on records which were obtained from the District Workmen's Sick Fund (*Ortskrankenkasse*) in an annual experience embracing nearly one million males and a quarter of a million females. For diabetes the number of cases and the number of deaths that occurred per 100,000 persons in the several age-groups are stated. Calculating, from the registered deaths in the English data, the number of cases that would occur at the several ages, if cases and deaths were in the same proportion as amongst the males in the Leipzig data, it is interesting to note that the average yearly number of cases from age 15 upwards that would be present in England and Wales in the period 1923-24 is 24,330. The correspondence between this result and that obtained by the use of Joslin's figures (the difference is only about 5 per cent. if allowance be made for the absence of males under 15 in the Leipzig data) seems to indicate that this number is more likely to represent a true estimate than that based on an average duration of three years. A rough approximation to the average annual number of diabetic cases in England and Wales in 1923-24 may thus be given pro-

³ *Krankheits- und Sterblichkeitsverhältnisse in der Ortskrankenkasse für Leipzig und Umgegend*, Band 2, p. 13. Bearbeitet im Kaiserl. Statist. Amt, Berlin, 1910.

visionally as 24,000. Computed on the same basis, the numbers in Scotland and in Ireland as a whole would be about 2,800 and 2,120 respectively, giving in round numbers 29,000 for the whole kingdom. Of this total about 12,150 or roughly 40 per cent. would be at ages 65 and upwards. From this estimate of the total diabetic population and the figures supplied by the Medical Research Council relating to the average weekly amount of insulin issued for use in the country as a whole at the half-yearly intervals from June 1923 onwards, and assuming that 15 units per day or 105 units per week is the average amount required per person, it is possible to estimate the proportion of the diabetic population that might be considered to be receiving adequate treatment by insulin if the whole amount issued were used for this purpose. The results are shown in Table V. Of a population of 29,000 diabetics at all ages the amount of insulin issued in December 1923 would supply 15 per cent.; in July 1924, 21 per cent.; in December 1924, 31 per cent.; and in December 1925, 38 per cent. If the use of insulin issued had been restricted to the diabetic population under 65 years of age, as the proportion over this age actually requiring it might be relatively small, the amount of insulin distributed was sufficient for 25 per cent. of these diabetics in December 1923, 53 per cent. in December 1924, and 65 per cent. in December 1925.

If, in place of 29,000, the diabetic population in the whole country⁴ were 15,600, that is the number based on a three years' average duration of the disease, the percentages of this population for which the supply of insulin issued in the different periods would have been sufficient are roughly double those given in the table. The percentages in Table V indicate the proportions of the diabetic population for which the supply of insulin would be adequate if the use of the substance were uniform throughout the country. It may be safely assumed, however, that insulin has been used remedially more extensively in London than elsewhere, next most commonly in county boroughs, where, as a rule, there are well-equipped hospitals, to a less extent in other urban districts which include the smaller towns, and least of all in the rural districts. These are points that must be considered in trying to interpret the varying decline in diabetic mortality that has taken place in different areas in the last three years. Another factor which probably influences the relative decline at different ages is that, as diabetes is well known to be more severe in young persons, and responds less well in these than in older persons to dietetic treatment, insulin would be used more extensively amongst the former. These assumptions in regard to procedure in this country seem to be borne out by the results of an investigation by the Metropolitan Life Insurance Company (1925) in America regarding the extent of the use of insulin in 1,800 fatal cases of diabetes mellitus among their industrial policy-holders in the year 1924. These deaths probably occurred in a population of lower average social status than the general population of diabetics in this country, but, for lack of other information, some facts elicited in this inquiry may be cited. It was found that less than half of the 1,800 fatal cases had

⁴ Including Ireland.

received insulin at any time, that the use of insulin was more general in urban than in rural communities, and that whereas fully 50 per cent. of the fatal cases in the cities had received insulin, the proportion in the distinctively rural areas was just over 40 per cent. Young persons were given insulin more extensively than older persons; over 70 per cent. of those less than 45 years of age, fully 50 per cent. of those between 45 and 64 years, and less than a third of those at 65 years of age and over had received insulin as a remedy.

In our results, the feature that immediately arrests attention is the relatively small divergence between the mortality-rates from diabetes in 1923-24 in the country as a whole and its main divisions generally, as well as in London in 1925, and the corresponding rates for the preceding years or what may be termed the pre-insulin period. Assuming that insulin has been used more extensively and perhaps more skilfully in London than elsewhere, it is indeed surprising that whereas in this city the mortality at all ages in 1923-24 is 28 per cent. lower in males and 16 per cent. lower in females than the corresponding rates in 1911-14, a similar decline in males, though not in females, is already apparent in the diabetic mortality for 1921-22, when insulin was still unavailable as a remedy. In the age-groups 25-44 and 45-64 the death-rates in males in London in 1923-24 have fallen 25 per cent. and 35 per cent. respectively, as compared with 1911-14, but these reductions in mortality are again only equal to those shown in 1921-22 and are practically the same as in the rural districts. Amongst females in London, the mortality in the age-group 25-44 in 1923-24 has apparently fallen to a somewhat greater extent than in males, but this age-group contains only 20 per cent. of the total deaths from diabetes. In the age-group 45-64, which contains nearly 40 per cent. of the total fatal cases from the disease, the female death-rate has fallen during the same period only 9 per cent., which is rather less than the decline shown in 1921-22, and has fallen to a similar extent in the rural districts. In the age-group 65 and upwards the mortality-rate in males in 1923-24 has fallen 14 per cent. as compared with 1911-14, whereas that in females remains unchanged. This feature is less remarkable than the relatively slight changes already described in the younger age-groups. The explanation probably lies in the fact that insulin is relatively less frequently administered to people at these higher ages, and that many of the registered deaths from diabetes at these ages are cases of glycosuria terminating fatally from arterio-sclerotic changes such as kidney disease, cerebral haemorrhage, or peripheral gangrene, and that treatment even with insulin has little influence in preventing these complications. As insulin is not a cure for diabetes, but only prolongs the lives of those suffering from the disease, in future years we may expect to find a relatively higher mortality in the highest age-groups, but it is too soon for any such effect to be responsible for the stability or even relative increase of diabetic mortality at ages 65 and upwards that is shown in some areas in 1923-24.

The more detailed mortality data for diabetes in London for the five individual years 1921 to 1925 (Table IV) provide material for serious thought. The numbers of deaths on which the mortality-rates for the selected age-groups

are based are certainly not large, but, as shown in the table, seem sufficient to warrant the suggestion that some confidence may be placed in the results. The standardized death-rates that are tabulated have also been recalculated, using populations which have been estimated by diverse methods, but the slight variations in the populations obtained by the different estimates make no appreciable changes in the rates that are given. The fact that, as compared with 1921, no apparent decline in the mortality from diabetes has taken place in London in 1924 amongst males at all ages or in any of the selected age-groups, if we disregard the relatively small reduction of 10 per cent. amongst those aged 45-64, cannot be regarded with equanimity. Amongst females in 1924 and also in 1923, a decline in mortality of 50 per cent. is shown in the age-group 25-44 as compared with 1921, but a fall of 30 per cent. is already evident in 1922 before insulin was available for treatment of the disease. The diabetic mortality-rate for persons in London in 1925, the most recent figures available, is not much more favourable than that for 1924. In persons at all ages the death-rate from the disease has only declined 13 per cent. as compared with the corresponding rate in 1921, and shows a like reduction amongst those at ages 45-64. Though amongst those at ages 25-44 a fall of 30 per cent. from the death-rate in 1921 is shown in 1925, the rate in this year remains practically the same as those in 1923 and 1924.

For the year 1925 no figures for any area of this country except London are obtainable at present, but it is interesting to note, from figures recently published in America by the Metropolitan Life Insurance Company (1926), that the death-rate from diabetes, which is based on fully 2,500 deaths amongst their industrial policy-holders, approximately 17 millions in number, after showing a decline in 1923 and 1924 coincident with the increasing use of insulin, has risen slightly in 1925, with the result that it has become identical with the mortality-rate for 1921. The mortality in the first quarter of the year 1926 also exceeds that in the corresponding part of the two previous years.

There is absolutely no doubt regarding the efficacy of the modern remedy, insulin, to prolong life in most cases of diabetes. Reports of numerous hospital cases bear testimony to the remarkable, indeed dramatic, results that follow its administration in cases of diabetic coma which till its advent almost invariably led to a fatal issue. Coma is said by Joslin (1924) to be the complication that leads to death in 66 per cent. of his long series of cases of diabetes that terminated fatally down to 1915. Amongst the certified deaths from diabetes in England and Wales in 1912 (Stevenson, 1914), coma was given as a complication in fully 40 per cent. As another 40 per cent. of the deaths were certified simply as diabetes without any further details, and coma was probably responsible for death in more than half of these, the real percentage of the mortality from coma amongst deaths in diabetics in this country is probably not very divergent from the figure given by Joslin. Joslin (1925) cites a hospital in which during a period of over two years only two deaths occurred out of 33 successive cases of diabetic coma treated by insulin, and states that it is now exceptional for

a patient in a hospital with diabetic coma to die. Nixon (1926) goes farther and states that since the introduction of insulin coma has become avoidable in practically every case of diabetes. It was about the middle of 1923 that MacLean (1923), in a discussion on 'Insulin in General Practice' at the Royal Society of Medicine, stated that insulin could be used with perfect safety by general practitioners; indeed it was their duty to use it. In the light of the results from the data for London and the other divisions of the country that are analysed in this paper, it is difficult to believe that insulin is being used to the best advantage in the treatment of diabetes. In seeking for an explanation as to why the decline in mortality from the disease since insulin was introduced has been so relatively slight, it may be pertinent to ask: Is insulin still only being used in many cases in the terminal stages of the disease when dietetic restrictions have been continued too long without any obvious response to such treatment? Are many diabetic patients who have been under treatment by insulin, with consequent rapid improvement, abandoning it but continuing with their more liberal diet in the belief that they are cured, though this is now known to be very improbable? While there is evidence, derived from a steadily increasing number of reported cases, that such an amelioration of the disease may occur after a varying course of insulin treatment as to permit of a considerable reduction in the dosage or even complete discontinuance of the remedy in certain cases, Harrison (1926) has come to the conclusion, from a prolonged study of a short series of cases, that insulin does not produce even a partial remission of the disease in the adult. Some results obtained in their analysis of fatal diabetic cases in America in 1924 by the Metropolitan Life Insurance Company, already referred to, shed light on some of these questions and strongly suggest that they must be answered in the affirmative. The outstanding observation in the inquiry was that insulin was given in the majority of these fatal cases in the very last stages of the disease. In other cases treatment by insulin had been begun and had produced rapid improvement, but was discontinued later by the patients in spite of the physicians' protests, and frequently with disastrous results. It may be suggested that the relatively high cost of the preparation in the earlier period precluded its use in many cases of the disease. Though this is not improbable, the effect may not have been so great as conjectured, as the incidence of diabetes is definitely highest amongst the better classes of the population.

Conclusions.

The results obtained by the analysis of the data from the several areas seem to indicate quite clearly that the death-rate from diabetes exhibited a definite tendency to decline in the years immediately preceding the introduction of insulin. This is very probably correlated with a better knowledge of appropriate methods of dietetic treatment. Taking these results and the facts that have been discussed into consideration, there is apparently very grave doubt as to whether the best possible use is being made of insulin in the treatment of

diabetes. Though other factors may have been operative in producing this state of affairs, there seems to be evidence to warrant the suggestion that, probably from some lack of appreciation by general practitioners of the valuable remedy for the disease at their disposal, and largely from lack of resolution on the part of those who suffer from the disease to persevere with the use of what is, at present, a somewhat irksome form of treatment, many valuable lives under the age of 65, that could most probably be prolonged, are still being lost to the community.

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TABLE I.

Showing the Standardized Death-rates from Diabetes per 1,000 amongst Males and Females at all Ages in England and Wales as a whole and London for various Periods of Years since 1881.

Period of Years.	Males.		Females.	
	England and Wales.	London.	England and Wales.	London.
1881-90	0.074	0.081	0.045	0.048
1891-1900	0.090	0.080	0.064	0.056
1901-10	0.104	0.106	0.084	0.078
1911-20	0.106	0.097	0.094	0.078
1911-14	0.116	0.109	0.099	0.089
1915-18*	—	—	0.093	—
1919-20*	—	—	0.086	—
1921-2	0.097	0.080	0.093	0.086
1923-4	0.089	0.079	0.092	0.075

* Where death-rates are omitted, the populations in the age-classes are not available.

TABLE II.

Showing the Standardized Death-rates from Diabetes per 1,000 amongst Males and Females at all Ages and in certain Age-groups in England and Wales and its principal Divisions for various Periods of Years since 1911.

Age Period.	Period of Years.	Males.					Females.				
		England and Wales.	London.	County Boroughs.	Urban Districts.	Rural Districts.	England and Wales.	London.	County Boroughs.	Urban Districts.	Rural Districts.
At all ages	1911-14	0.116	0.109	0.121	0.121	0.109	0.099	0.089	0.097	0.102	0.105
	1911-20	0.106	0.097	0.111	0.108	0.099	0.094	0.078	0.092	0.092	0.093
	1921-22	0.097	0.080	0.097	0.105	0.095	0.093	0.086	0.093	0.096	0.097
	1923-24	0.089	0.079	0.091	0.094	0.086	0.092	0.075	0.094	0.098	0.091
From 25 to 44 years	1911-14	0.072	0.059	0.073	0.069	0.085	0.058	0.055	0.053	0.057	0.073
	1911-20	0.073	0.053	0.072	0.071	0.078	0.056	0.049	0.054	0.056	0.066
	1921-22	0.067	0.044	0.064	0.073	0.073	0.057	0.050	0.057	0.057	0.064
	1923-24	0.049	0.044	0.042	0.053	0.059	0.045	0.030	0.046	0.047	0.050
From 45 to 64 years	1911-14	0.283	0.296	0.288	0.305	0.240	0.260	0.246	0.267	0.267	0.231
	1911-20	0.254	0.244	0.259	0.248	0.211	0.237	0.209	0.240	0.234	0.203
	1921-22	0.211	0.187	0.208	0.230	0.198	0.225	0.206	0.233	0.231	0.215
	1923-24	0.194	0.191	0.205	0.205	0.165	0.231	0.223	0.235	0.248	0.209
65 years and upwards	1911-14	0.872	0.835	0.993	0.947	0.709	0.716	0.642	0.696	0.781	0.692
	1911-20	0.808	0.754	0.873	0.830	0.638	0.684	0.561	0.653	0.691	0.626
	1921-22	0.711	0.691	0.744	0.765	0.651	0.676	0.698	0.686	0.704	0.619
	1923-24	0.782	0.720	0.863	0.830	0.679	0.764	0.637	0.828	0.791	0.707
Average annual number of recorded deaths from diabetes	1911-14	2093	231	625	742	494	2087	236	606	743	502
	1923-24	1912	196	608	675	433	2399	243	783	867	511

TABLE III.

Showing the Standardized Death-rates from Diabetes per 1,000 amongst Males and Females at all Ages and in certain Age-groups for England and Wales and its Divisions, London, County Boroughs, Urban Districts, and Rural Districts in 1911-20, 1921-22, and 1923-24, expressed as Percentages of the Corresponding Death-rates in the Four-yearly Period 1911-14.

Age Period.	Period of Years.	Males.					Females.				
		England and Wales.	London.	County Boroughs.	Urban Districts.	Rural Districts.	England and Wales.	London.	County Boroughs.	Urban Districts.	Rural Districts.
At all ages	1911-14	100	100	100	100	100	100	100	100	100	100
	1911-20	91	89	92	89	91	94	88	95	90	89
	1921-22	84	73	80	87	87	93	97	96	94	92
	1923-24	77	72	75	78	79	92	84	97	96	87
From 25 to 44 years	1911-14	100	100	100	100	100	100	100	100	100	100
	1911-20	101	90	99	103	92	97	89	102	98	90
	1921-22	93	75	88	106	86	98	91	108	100	88
	1923-24	68	75	58	77	69	78	55	87	82	68
From 45 to 64 years	1911-14	100	100	100	100	100	100	100	100	100	100
	1911-20	90	82	90	81	88	91	85	90	84	88
	1921-22	75	63	72	75	83	87	84	87	87	93
	1923-24	69	65	71	67	69	89	91	88	93	90
65 years and upwards	1911-14	100	100	100	100	100	100	100	100	100	100
	1911-20	93	90	88	88	90	96	87	94	88	90
	1921-22	82	76	75	82	92	94	109	99	90	89
	1923-24	90	86	87	89	96	107	99	119	101	102

TABLE IV.

Showing the Standardized Death-rates from Diabetes per 1,000 at all Ages and in certain Age-groups in London for the Individual Years 1921 to 1924, in the Separate Sexes; and the Years 1921 to 1925 for Persons; and the Death-rates in these Groups in the Years 1922 to 1925 expressed as Percentages of the Corresponding Death-rates in 1921.

Year.	Males.				Females.				Persons.			
	Age-groups.				Age-groups.				Age-groups.			
	All Ages.	25-44.	45-64.	65 and upwards.	All Ages.	25-44.	45-64.	65 and upwards.	All Ages.	25-44.	45-64.	65 and upwards.
1921	0.073	0.085	0.195	0.528	0.083	0.059	0.193	0.635	0.079	0.048	0.195	0.590
1922	0.087	0.054	0.179	0.730	0.088	0.041	0.218	0.760	0.087	0.047	0.200	0.747
1923	0.083	0.045	0.204	0.763	0.073	0.030	0.239	0.524	0.077	0.036	0.223	0.623
1924	0.075	0.042	0.175	0.674	0.078	0.029	0.207	0.747	0.076	0.035	0.192	0.713
1925	—	—	—	—	—	—	—	—	0.069	0.033	0.170	0.670
1921	100	100	100	100	100	100	100	100	100	100	100	100
1922	119	154	92	138	106	69	113	120	110	98	103	127
1923	114	129	105	145	88	51	124	83	97	75	114	106
1924	103	120	90	128	94	49	107	118	96	73	98	121
1925	—	—	—	—	—	—	—	—	87	69	87	114
Average annual number of recorded deaths for the period 1921-24	200	30	80	75	250	30	105	105	450	60	185	180

TABLE V.

Showing at Half-yearly Intervals, from June 1923 onwards, the Proportions of the estimated Diabetic Population in Great Britain for which Treatment might be provided by the amount of Insulin issued by British Firms.

Period.	Average number of units issued per week for use in Great Britain (four-weekly averages).	Number of persons provided for on allowance of 105 units per person per week.	Percentage of diabetic population of 29,000 at all ages provided for.	Percentage of diabetic population of 16,900 under age 65 provided for if use of insulin were restricted to those under this age.
June 1923	151,317	1,441	5	9
December 1923	448,025	4,267	15	25
July 1924	654,025*	6,229	21	37
December 1924	947,175*	9,021	31	53
July 1925	974,525*	9,281	32	55
December 1925	1,158,208*†	11,031	38	65

* The amounts exported are deducted.

† Weekly average based on last 13 weeks of year 1925.

THE BROMSULPHALEIN TEST OF LIVER FUNCTION

A CLINICAL STUDY OF SIXTY-SIX CASES¹

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Introduction.

THE bromsulphalein test of liver function was introduced by Rosenthal in 1924 as an improvement upon the phenoltetrachlorophthalein test which he had previously perfected and simplified for clinical use. The disadvantages of the latter were sufficient to preclude its general adoption as a routine clinical measure. The concentration it reaches in the blood never exceeds 35 per cent.; the amount of dye used is large—5 mg. per kilo body-weight; and the extremely irritant properties of the dye frequently result in venous thrombosis, phlebitis, and systemic reactions. Piersol and Bockus (1) had five cases of venous thrombosis in sixty-seven injections, and early in 1923, before he realized the dangerous properties of the dye, the writer had two similar accidents in four injections. Rowntree, Hurwitz, and Bloomfield (2) reported one case of sudden unexplained death six days after the injection; Maurer and Gatewood (3) reported three deaths in their series two to seven days after the test—two of these cases showed recent thromboses. Rosenau (4) has described constitutional disturbances in the way of rigors, hepatic pain, and prolonged purgation, whilst Ottenberg and Abramson (5) have demonstrated the occurrence in rabbits of necroses in the liver, spleen, and kidneys after the use of the dye.

The bromsulphalein test is free from most of these objections—the concentration in the serum reaches a high percentage, the amount used is only 2 mg. per kilo, and the dye is non-irritant.

The History of the Test.

Bromsulphalein or phenoltetrabromphthalein sodium sulphonate was prepared by White; it is very readily soluble in water, and it can be given with impunity in concentrated solution by the intravenous route—intramuscular injections are not advisable, as they may be followed by cellulitis. The first

¹ Received May 27, 1926.

mention of the test founded upon the use of this dye is in a paper by Rosenthal (6) quoting the results of certain favourable animal experiments he had made. In a later communication by Rosenthal and White (7) the subject is amplified.

A research was made into the pharmacology of certain of the phthaleins, and into their value in the estimation of hepatic function, chiefly by animal experiment. As regards the latter it was found that the sulphonated phthaleins were the most suitable members of the group, and some of the facts concerning their behaviour must be given.

After intravenous injection they appear in the urine in minute traces, but their excretion by the bile is very rapid; they appear in four minutes, and at the end of an hour 72 per cent. is excreted by this route. After the injection of 5 mg. per kilo body-weight the blood-serum contains 29 per cent. after three minutes, and a mere trace after fifteen minutes. The toxicity of the dyes is low, and it was found that doses of 50 mg. per kilo produced death exceptionally, under 100 mg. per kilo the symptoms were not usually more than a fleeting rigor, whilst over this dosage death was produced in 50 per cent. of cases by convulsions. The post-mortem findings were not striking. Bromsulphalein was non-haemolytic to washed rabbits' red corpuscles in concentrations of 50 mg. in 15 c.c. of normal saline solution. This member of the group was considered to be most favourable for the purpose of estimating liver efficiency, and intensive experimental work was undertaken to establish its claims and to compare it with phenoltetrachlorphthalein.

The liver of the rabbit consists of two unequal lobes which can be ligated separately—ligation of the main lobe deprives the animal of 80 per cent. of its liver tissue. It was shown that the concentration of the dye in the serum after half an hour was equal to the amount of the liver tissue removed:

Concentration of the dye in the blood after 5 mg. per kilo.

	%	%	%	%	%	%
<i>Normal</i>	31	2	0	0	0	0
<i>Main lobe ligation</i>	96	87	72	63	43	33
	3 min.	15 min.	30 min.	60 min.	120 min.	180 min.

In a further paper Rosenthal and White (8) outline their technique and record their clinical findings—they conclude that the test is accurate and much superior to the phenoltetrachlorphthalein test.

Technique.

The patient is weighed and the dosage is calculated on a basis of 2 mg. of the dye per kilo body-weight. The body-weight of the patient in pounds divided by 55 will give the exact quantity in cubic centimetres of the 5 per cent. solution required. It may be measured by drawing it directly into a 5 c.c. syringe and then injected slowly into an arm vein; the injection should occupy one minute. Thirty minutes after the injection a sample of blood (4.5 c.c.) is withdrawn,

preferably from the opposite vein, and in cases of early liver disease it may be necessary to take a sample after five minutes.

After the blood has coagulated it is centrifugalized and the clear serum is pipetted into two small test-tubes. To one of these is added one to two drops of a 10 per cent. solution of sodium hydroxide to bring out the colour of the dye, and to the other tube a drop of 5 per cent. hydrochloric acid to clear the serum of any haemolysis. The amount of dye present is now estimated by direct comparison with a series of standards, using a simple comparator box in the usual way. The standards may be prepared by adding 4 mg. of the dye to 100 c.c. of water that has been alkalized with 0.25 c.c. of a 10 per cent. solution of sodium hydroxide. This represents the 100 per cent. standard, and the others can be made by diluting with the alkalized water. Ten such standards are made ranging from 10 per cent. to 100 per cent., and c.c. of each are sealed off in small test-tubes—no deterioration will take place in the colour for several months if they are kept in the dark.

The 100 per cent. standard represents the amount of the dye that would be present in the blood-serum if none were removed; it is thus an arbitrary standard calculated on blood-volume.

Clinical Findings.

The clinical findings of Rosenthal and White were as follows: in twelve patients with acute or chronic gonorrhoea, eleven patients with disease not affecting the liver, and in two cases of chronic nephritis 20 to 50 per cent. of the dye was present in the serum five minutes after the injection, and none or a mere trace after thirty minutes. In the urine there was a small amount ranging from nothing to 0.5 per cent. of the amount injected. In liver disease the criterion was the percentage of the dye in the serum after the half-hour period, and this figure was taken to represent the degree of functional insufficiency. Their results are set out in the following table:

Case.	Diagnosis.	5 min. %	30 min. %
1.	Metastatic cancer of the liver	100	99
2.	Cancer of pancreas—obstr. jaundice	100	97
3.	Gall-stones—obstr. jaundice	100	96
4.	"	?	90
5.	Catarrhal jaundice	100	75
6.	"	?	50
7.	Arsphenamine jaundice	?	47
8.	Biliary cirrhosis	?	45
9.	Gall-stones—obstr. jaundice	95	35
10.	Catarrhal jaundice—mild	?	35
11.	Portal cirrhosis—early	65	?
12.	Acute cholecystitis—obstr. jaundice	65	30
13.	Pre-eclamptic toxæmia	55	30
14.	Portal cirrhosis	?	22
15.	Metastatic cancer of liver	55	20
16.	Portal cirrhosis	55	17
17.	Gall-stones—acute cholecystitis	90	10
18.	" chronic "	65	5
19.	Syphilitic cirrhosis	50	3
20.	Arsphenamine jaundice	?	22 (15 min.)

Cases 1, 3, 4 died in 8, 4, and 14 days after the test.

Personal Experiences.

At the outset of the research at the beginning of 1925 very considerable difficulty was experienced in obtaining a supply of bromsulphalein in this country. It was considered inconvenient to import it directly from the American manufacturers—Messrs. Westcott, Hynson, and Dunning, of Baltimore—owing to the unavoidable delay in getting fresh supplies. Ultimately Messrs. Martindale and Westcott, of London, made the dye themselves, and an adequate amount was always obtainable without delay. The dye was put up in glass ampoules containing 3 c.c. of a 5 per cent. solution sterilized.

Technique.

The technique was virtually that of Rosenthal and White which is described above. The calculated amount of the dye was measured in a special 5 c.c. syringe graduated in one-tenths of a cubic centimetre and injected into an arm-vein; it was not considered necessary to subject the patient to the pain of withdrawing a blood sample after five minutes, and the estimation was performed upon a single specimen taken after thirty minutes from the opposite arm. This precaution was adopted with a view to eliminating the error that might be introduced by using the blood from a possibly dye-impregnated vein.

The blood was allowed to clot spontaneously, and the serum was centrifugalized; about 2 c.c. were then placed in each of two small, narrow test-tubes.

The series of standards was prepared on the same lines as those of Rosenthal and White, and the successive dilutions were sealed in small test-tubes of the same size as those in which the serum had been placed. A point of some practical importance presented itself at this stage, as it was found that if the dye standards were placed in the test-tubes and the necks of the tubes sealed in a blow-pipe flame the dye lost colour or the colour was sometimes altered. At the suggestion of Dr. W. T. Hillier, Clinical Pathologist to the General Hospital, Birmingham, a manœuvre was used which overcame this difficulty. The test-tubes were drawn out in a blow-pipe flame into long necks like those of vaccine bottles, the closed ends of the tubes were heated, and the necks were plunged into the dye; by contraction of the volume of the contained air the fluid was slowly drawn up and it was not subjected to sufficient heat to cause any loss of colour. The necks of the tubes were then sealed up in the usual way and the tubes marked with a diamond.

The actual estimations of the dye percentages of the sera were kindly carried out by Dr. Hillier, who was purposely kept in ignorance of the nature of the cases—a very valuable unbiased control of the results being thus assured. To one of the test-tubes containing serum four drops of a 5 per cent. solution of NaOH were added, to the other a similar volume of distilled—a stronger solution such as that used by Rosenthal and White was found to coagulate the protein in the serum and to vitiate the results. The dye percentages were ascertained

by direct comparison in a comparator box; a tube of water was placed behind the serum to which the alkali had been added, and a tube of a dye dilution was placed behind the colourless serum. Dr. Hillier experienced little difficulty in matching the colours, although in some cases the colours were unmatchable, owing, perhaps, to slight haemolysis. These results were discarded.

Reactions.

In spite of the occasional escape of dye into the subcutaneous tissues no local reactions took place. In a few children, who are not included in this series, the injection was almost entirely subcutaneous, as the technical difficulties of venepuncture proved insuperable; none of them had any local reaction, although no precautions were taken to avoid it in the way of hot fomentations, &c.

In the majority of the cases no discomfort was experienced. Three or four of the patients complained of a fleeting feeling of 'light-headedness' immediately after the injection; several of them reported the occurrence of purgation for a few days afterwards, and it was found that this symptom was practically confined to very heavy persons who had received a large amount of dye. The only alarming general reaction occurred in the women in one particular ward; immediately after the injection one patient complained of very acute pain in the region of the sacrum; each patient who was used during the next few days developed similar symptoms, and one of them almost fainted. The ward Sister's suggestion that this was purely an imaginary complaint was shown to be true by the complete absence of such an occurrence in the ward after the generation of patients who fostered the tradition had left hospital.

The writer can, therefore, confirm the claims made that bromsulphalein in doses of 2 mg. per kilogram of body-weight is non-irritant and innocuous, apart from the occasional occurrence of purgation in heavy patients who have received a large dose of the dye.

Results.

The results of the tests on the whole were disappointing, and although an endeavour was made to exclude causes of experimental error by a careful standardization of each step in the technique, a peculiarly variable series of findings was obtained.

The normal cases varied from 5 to 45 per cent., and no cause could be discovered for this; the only respect in which the normal subjects differed from the other cases was the fact that they were not confined to bed, and that during the course of the tests they were moving about and doing their usual duties in the wards (they were recruited from the resident medical staff of the Hospital). It would seem unwise to suggest that the liver only performs its functions to perfection under conditions of rest, and that moderate exercise in an upright position can cause it to default to the extent of 45 per cent.

The non-liver cases were likewise variable, ranging from a complete removal of the dye from the blood to a retention of 35 per cent.; it is remarkable that the variation was less than in the normal cases.

By using cases of blood diseases it was thought that mild degrees of liver dysfunction might be encountered as the result of the degenerations and infiltrations which are known to occur in these conditions. The variations from Rosenthal and White's normal were not, however, considerable.

The nephritic cases require little comment; the one in which the liver might be expected to be damaged (Case 36) showed a higher degree of retention than the other case.

In the cardiac group two cases were compensated, and they showed a retention of 10 and 20 per cent.; two cases of cardiac failure showed a dye percentage which was compatible with the degree of liver insufficiency that might be inferred from clinical grounds; one case of cardiac failure had a lower dye retention than the compensated cases.

The two cases of doubtful toxæmias of pregnancy were, from the clinical point of view, so indefinite as to arouse doubts as to the possibility of so great a degree of liver insufficiency as they showed.

The cases of obstructive jaundice were of great interest as the dye retention was almost complete; that two of them showed a retention of over 100 per cent. merely suggests that the blood-volume of the patients was altered or that it did not conform to the calculation for blood-volume upon which the 100 per cent. standard was fixed by Rosenthal and White. Clinically the patients were comparatively well, and their chief complaints were pruritus and the somewhat unusual aesthetic effect of an icteric complexion. It is very tempting to infer that the dye retention was due to biliary impermeability and not to hepatic insufficiency. This possibility has been repeatedly denied by Rosenthal in the case of the phenoltetrachlorphthalein test, but in a recent paper Snell, Greene, and Rowntree (9) have shown experimentally that in the case of this substance dye retention and bile retention run parallel after ligation of the common bile-duct, and that both occur more rapidly after the additional operation of cholecystectomy.

Catarrhal jaundice gave results which were roughly compatible with the clinical severity of the cases.

In atrophic cirrhosis of the liver the retention was high only in one case which was not severe clinically; the results were on the whole similar to those obtained by Rosenthal and White.

Case 59 showed a retention much in excess of what would have been foretold by other methods.

The other cases gave results which were quite compatible with the clinical facts.

Criticism.

With regard to the technique of the test the only criticism that can be offered is common to all colorimetric methods, that is, the introduction of a big personal factor in colour matching. The results of different workers are thus rendered difficult of comparison, and the results of the same worker are subject to some variation.

In order to criticize the actual results obtained it is only necessary to scan the appended table (see p. 113), and whilst it is obvious that the majority of the cases show dye retentions which are compatible with clinical facts, at least 20 per cent. of them do not reflect the degree of liver insufficiency. If a test of liver function is to be of value it must not be subject to this degree of error, or of anomalous results, otherwise the results of any one estimation will defy interpretation.

Conclusions.

1. The test is a simple one, and is innocuous to the patient.
2. It is objectionable because it depends upon colorimetry.
3. Twenty per cent. of the cases give results which are obviously not representative of the degree of liver efficiency; the rest are acceptable.
4. In obstructive jaundice the results suggest that the test is one of biliary permeability and not of liver efficiency.

*Cases.**Normal cases—ten.*

These were all in healthy young adults of both sexes, their ages ranging from 21 to 29 years, and the dye retention from 5 to 45 per cent.

Non-Liver cases—fourteen.

Case 11. Mrs. Louisa J., aged 47 years. The patient had a right-sided hydronephrosis, and she was quite well apart from the dragging pain in the loin. Bromsulphalein retention of 10 per cent.

Case 12. Louisa P., aged 26 years. This was a case of mild acholuric jaundice of the familial splenomegalic type, the liver was not enlarged, and the anaemia was not of a marked degree. Bromsulphalein retention of 10 per cent.

Case 13. Mary R., aged 19 years. The patient had been in hospital several times for the treatment of diabetes mellitus; the last admission was on account of incipient coma. At the time of the test she had emerged from her drowsy state, but the urine contained sugar and ketone bodies. Bromsulphalein retention of 10 per cent.

Case 14. Mrs. Wh., aged 46 years. A case of diabetes mellitus not quite sugar free on 1,900 calories and 5 units of insulin a day. Bromsulphalein retention of 20 per cent.

Case 15. Mrs. S., aged 53 years. Diabetes mellitus sugar free on 1,900 calories and 5 units of insulin a day. Bromsulphalein retention of 35 per cent.

Case 16. Nellie C., aged 14 years. The patient had a unilateral tremor and the typical gait and facies of post-encephalitic parkinsonism of one year's duration. Bromsulphalein retention of 10 per cent.

Case 17. James P., aged 50 years. The patient had reported for indefinite indigestion; a lump was found in the epigastrium which at operation was discovered to be an inoperable cancer of the body of the stomach; there were no metastases in the liver. The test was done prior to operation. Bromsulphalein retention of 30 per cent.

Case 18. George S., aged 41 years. The patient was quite fit apart from a duodenal ulcer and hyperchlorhydria. Bromsulphalein retention of a trace.

Case 19. Herbert G., aged 35 years. The patient had a myopathy of the right quadriceps femoris muscle, otherwise he was normal. Bromsulphalein retention of 4 per cent.

Case 20. Harry K., aged 21 years. Healthy apart from a simple hyperchlorhydria. Bromsulphalein retention of a mere trace.

Case 21. Mrs. E., aged 61 years. Mild dyspepsia, otherwise the patient was quite healthy. Bromsulphalein retention of 5 per cent.

Case 22. John F. Sciatica, otherwise the patient was healthy. Bromsulphalein retention nil.

Case 23. Mary S., aged 36 years. The patient had a marked parkinsonian syndrome following encephalitis lethargica. She was very dull mentally, and was continually salivating. Bromsulphalein retention of 10 per cent.

Case 24. John S., aged 51 years. Similar to 23. Bromsulphalein retention of 10 per cent.

Blood diseases—ten cases.

Case 25. May D., aged 30 years. The patient had Hodgkin's disease with enlargement of the spleen and lymphatic glands of the neck, and her temperature was of the Pel-Epstein type. The liver was not involved. Reds 3,900,000; whites 19,200; Hb. 52 per cent.; polymorphs 80 per cent. Bromsulphalein retention of 30 per cent.

Case 26. Henry H., aged 30 years. The patient had chronic myelogenous leukaemia, with enormous enlargement of the spleen; the liver was normal in size—he was not ill and was working up to the time of his admission. Reds 4,220,000; whites 150,000; Hb. 75 per cent.; the film showed 35 per cent. of myelocytes. Bromsulphalein retention of a trace.

Case 27. Elsie C., aged 2 years. The child had a severe anaemia with enlargement of the spleen, the liver being normal in size; as no cause was discoverable the case was diagnosed as anaemia gravis. Reds 2,000,000, whites 18,000. Bromsulphalein retention of 25 per cent.

Case 28. Mrs. R., aged 29 years. Secondary anaemia of the chlorotic type following lactation. Bromsulphalein retention of 25 per cent.

Case 29. Hilda M., aged 9 years. The child was a member of a family two members of which had had splenic anaemia. She had a moderate splenomegaly, but no anaemia; and she was regarded as being in the first stage of splenic anaemia. Bromsulphalein retention of 30 per cent.

Case 30. John W., aged 68 years. The patient was admitted on account of progressive anaemia and asthenia; he had a moderate splenomegaly and a small spleniculus was palpable below the spleen, the liver was not enlarged. Reds

4,560,000; whites 10,400 (lymphocytes 86 per cent.); Hb. 73 per cent. Lymphatic leukaemia. Bromsulphalein retention of 15 per cent.

Case 31. Joseph R., aged 12 years. The patient was of a subicteric hue, he had a marked secondary anaemia with slight splenomegaly, the liver was not enlarged. Reds 2,600,000; whites 7,200; he was regarded as a splenic anaemia in the second stage. Bromsulphalein retention of 15 per cent.

Case 32. John P., aged 52 years. The patient had had pernicious anaemia since 1921 with achlorhydria, and absence of enlargement of the liver and spleen; reds 1,700,000; whites 6,000; Hb. 50 per cent.; C. I. 1.3. The blood gave the typical picture of pernicious anaemia and the van den Bergh reaction gave a delayed direct result. Bromsulphalein retention of 35 per cent. on 25.8.25, three days after 0.3 gm. of novarsenobillon; on 5.10.25 after five injections of novarsenobillon the patient's progress was retrograde and the retention was 25 per cent.

Case 33. Beatrice B., aged 20 years. This was a very chronic case of myelogenous leukaemia; the spleen was one inch below the costal margin, the liver was impalpable. Reds 3,956,000; whites 102,900. Bromsulphalein retention of 20 per cent.

Case 34. Sarah W., aged 12 years. This was a fairly acute case of lymphatic leukaemia of six months' duration; there was profound anaemia, and enlargement of the glands of the neck, axillae, and groins, with marked splenomegaly; the liver was normal in size. Reds 1,500,000; whites 19,000 (lymphocytes 90 per cent.). No bromsulphalein retention.

Nephritis—two cases.

Case 35. George M., aged 29 years. The patient had an acute exacerbation of a chronic interstitial nephritis with blood, albumin, and casts in the urine. At the time of the test there was no oedema and the liver was not palpable. Bromsulphalein retention of 10 per cent.

Case 36. St. Valentine S., aged 53 years. The patient had chronic interstitial nephritis with severe cardiorenal failure, oedema of the legs, ascites, orthopnoea, and enlargement of the liver; B. P. 180/146. Bromsulphalein retention of 30 per cent.

Cardiac cases—five.

Case 37. Leonard B., aged 57 years. Aortic stenosis and incompetence with cardiac failure—liver enlarged to one finger's breadth below the costal margin, orthopnoea, no oedema. Bromsulphalein retention of 5 per cent.

Case 38. Mrs. A., aged 43 years. The patient came into hospital with a huge heart, mitral incompetence, and auricular fibrillation. At the time of the test the compensation had been almost completely restored. Bromsulphalein retention of 10 per cent.

Case 39. John E., aged 38 years. The patient had auricular fibrillation and ulcerative endocarditis with embolic phenomena. The cardiac lesions were those of mitral disease; at the time of the test the heart was well under digitalis and no oedema was present. The liver was normal in size. Bromsulphalein retention of 20 per cent.

Case 40. Florence D., aged 26 years. The patient had mitral and aortic disease with auricular fibrillation and severe cardiac failure. She was very cyanosed, the liver was enlarged three fingers' breadths below the costal margin, and she had slight jaundice. The urine contained bile-salts and pigments. Bromsulphalein retention of 40 per cent.

Case 41. Mrs. S., aged 33 years. The patient had aortic disease with cardiac failure—ascites and enlargement of the liver on dipping for it. The urine contained bile-salts and pigments, and the van den Bergh reaction was biphasic in the serum. Bromsulphalein retention of 60 per cent.

Doubtful toxæmias of pregnancy—two cases.

Case 42. Mrs. P., aged 33 years. The patient, six months pregnant, was admitted with lower abdominal pain, headaches, and vomiting. The urine did not contain any abnormal constituents. Three days after admission the test was done and the symptoms had disappeared. Bromsulphalein retention of 40 per cent.

Case 43. Mrs. P., aged 40 years. The patient, seven months pregnant, was admitted complaining of severe frontal headache; the urine contained bile-salts, pigments, and urobilin. She was regarded as a mild hepatic toxæmia. Bromsulphalein retention of 35 per cent.

Obstructive jaundice—three cases.

Case 44. John E., aged 35 years. The patient had a complete obstructive jaundice of seven weeks' duration with enlargement of the liver three fingers' breadths below the costal margin. At operation a carcinoma of the head of the pancreas was found. The bromsulphalein retention prior to operation was 110 per cent.

Case 45. Cecil L., aged 29 years. An absolutely similar case to the above, confirmed by operation. Bromsulphalein retention 140 per cent.

Case 46. Mrs. M., aged 45 years. The common bile-duct had apparently been injured during an operation for cholecystectomy and the patient developed a complete obstructive jaundice. Bromsulphalein retention of 100 per cent.

Acute hepatitis—catarrhal jaundice, &c.—six cases.

Case 47. May S., aged 6 years. The test was done on the fourth day of a mild catarrhal jaundice; the liver was enlarged to three fingers' breadths below the costal margin. Bromsulphalein retention of 30 per cent.

Case 48. Hughes (f.), aged 4 years. The test was done on the fourth day of a mild catarrhal jaundice; the liver was enlarged to three fingers' breadths below the costal margin, the skin and mucosae were icteric, but the stools were not completely decolorized—the van den Bergh reaction was biphasic. The jaundice was clear by the ninth day. Bromsulphalein retention of 20 per cent.

Case 49. John T., aged 30 years. The patient was admitted with a complete jaundice and hepatic pain accompanied by pyrexia and rigors, the liver was enlarged to three fingers' breadths below the costal margin, and there was a pleural friction rub over the right lower ribs. The van den Bergh reaction gave a delayed direct result. The bromsulphalein retention at this time was 70 per cent. At operation a suppurating hydatid cyst of the liver was found.

Case 50. Dorothy P., aged 9 years. The patient had catarrhal jaundice of nine days' duration, the spleen was palpable, the liver was enlarged to two fingers' breadths below the costal margin, but the stools were not completely decolorized. Bromsulphalein retention of 100 per cent. The jaundice cleared on the seventeenth day.

Case 51. George C., aged 40 years. The patient was recovering from the acute phase of a subacute liver atrophy following novarsenobillon; the icterus, although well marked, was disappearing. Bromsulphalein retention of 20 per cent.

Case 52. Hilda G., aged 16 years. The patient had just recovered from an acute delirium accompanying a very severe catarrhal jaundice; she had had jaundice for seven days, and the stools were clay coloured. The van den Bergh reaction gave a delayed direct result. Two tests were done on different days of the disease. (1) Seventh day, a retention of 80 per cent. (2) Nineteenth day—jaundice present only in the conjunctivae—a retention of 10 per cent.

Cirrhosis of the liver (Laennec's)—six cases.

Case 53. Edward F., aged 53 years. The patient had a gross and recurring ascites with the liver enlarged to four fingers' breadths below the costal margin; the Wassermann reaction was strongly positive. A laevulose tolerance test gave a normal result as follows: before levulose the blood-sugar was 0.120 per cent., at half-hour periods after 50 grm. of the sugar it was 0.105, 0.103, 0.103, and 0.105 per cent. The bromsulphalein retention was 30 per cent.

Case 54. Mrs. B., aged 44 years. In 1919 the patient had an operation for symptoms of chronic appendicitis and nothing but cirrhosis of the liver was found; in 1921 she had a haematemesis, and she had not been well since. During the four months prior to the test she had dyspnoea on exertion and oedema of the legs. The liver was palpable three fingers' breadths below the costal margin; it was hard; there was no ascites. The urine contained small quantities of bile-salts and pigments. Bromsulphalein retention of 40 per cent.

Case 55. Walter S., aged 63 years. The patient had a cirrhosis of the liver with enlargement to four fingers' breadths below the costal margin. He had chronic bronchitis with marked emphysema and orthopnoea. The bromsulphalein retention was 60 per cent.

Case 56. Mrs. O., aged 46 years. The patient had a cirrhosis of the liver with recurrent attacks of acute hepatitis with jaundice. The test was done during one of these attacks. The liver was enlarged to four fingers' breadths below the costal margin, and she had a slight jaundice. Bromsulphalein retention of 25 per cent.

Case 57. Harry F., aged ? years. The patient had an alcoholic cirrhosis of the liver with gross ascites, oedema of the legs, and dyspnoea. At the time of the test he was convalescent and the ascites had subsided. Bromsulphalein retention of 12 per cent.

Case 58. William D., aged 34 years. The patient had dermatitis herpetiformis, and for 2½ years he had received 5 minims of liquor arsenicalis t. d. s.; during the few months prior to admission he had developed arsenical pigmentation of the skin and a gross ascites. The Wassermann reaction was negative, and a diagnosis of atrophic cirrhosis of the liver due to arsenic was made. The urine contained bile-salts, pigments, and urobilin in minimal amounts, the van den Bergh reaction gave a feeble indirect result. A laevulose tolerance test gave the following result: before the test the blood-sugar was 0.095 per cent., at half-hourly intervals after 50 grm. of laevulose it was 0.102, 0.100, 0.116, and 0.100 per cent. Bromsulphalein retention 18.8.25—22 per cent.; 31.8.25—20 per cent.; 28.10.25—20 per cent. The patient improved very greatly under treatment.

Doubtful cirrhosis of the liver (Laennec's type)—one case.

Case 59. Herbert B., aged 52 years. The patient was admitted for the investigation of liver pain. Physical examination revealed nothing. The ultimate diagnosis was a doubtful early cirrhosis with perihepatitis causing pain. Bromsulphalein retention of 65 per cent.

Mild acute cholecystitis—one case.

Case 60. Samuel M., aged 65 years. The patient was admitted with chronic mild rheumatoid arthritis and he developed a mild attack of cholecystitis. At the time of the test he was free from pain and jaundice. Bromsulphalein retention of 10 per cent.

Suppurative pylephlebitis—one case.

Case 61. Mrs. H., aged 31 years. The patient was admitted on account of rigors for three weeks following an abortion. Two days before admission she developed jaundice of a moderate degree. She died a week after admission and at the autopsy a suppurative pylephlebitis was found secondary to pelvic thrombophlebitis. The bromsulphalein test on admission showed a retention of 40 per cent.; the van den Bergh reaction gave a marked biphasic response.

Doubtful Hanot's cirrhosis—two cases.

Case 62. B. (male), aged 37 years. The patient had a massive hepatomegaly of two years' duration of unknown origin, with slight jaundice and bile-salts and pigments in the urine; the van den Bergh reaction gave a biphasic response. The diagnosis of Hanot's cirrhosis was very dubious. Bromsulphalein retention of 65 per cent.

Case 63. Stephen B., aged 4 years. The patient was admitted with the history of recurrent attacks of jaundice, hepatomegaly, and splenomegaly for two years. At the time of the test he was convalescent from such an attack; he had a slight icteric staining of the conjunctivae, but the liver and spleen were not palpable. The Wassermann reaction was strongly positive, the van den Bergh test gave a faint indirect reaction, and the urine contained bile-salts. The bromsulphalein retention was 5 per cent.

Amyloid disease—one case.

Case 64. John T., aged 12 years. The patient had a double psoas abscess secondary to spinal caries; it had been discharging for six years. He was admitted with waxy disease of the liver and spleen, and it was doubtful whether or not the kidneys were affected. The bromsulphalein retention was 25 per cent.

Haemochromatosis—one case.

Case 65. Fred W., aged 44 years. The patient was admitted with diabetes mellitus, an enlarged liver, and pigmentation of the skin. The liver was enlarged to four fingers' breadths below the costal margin. The bromsulphalein retention was 20 per cent.

Carcinoma of the suprarenal body—one case.

Case 66. Hilda A., aged 21 years. The patient was admitted as for the previous twelve months she had lost her female secondary characteristics, and had developed a profuse beard and become very fat. On examination the liver was found to be enlarged upwards, but at the time of the test there was little else to be made out. Bromsulphalein retention of 25 per cent. She developed a thrombosis of the right femoral vein, jaundice, &c., and died six weeks later. At the autopsy a carcinoma of the right suprarenal body was found with direct invasion of the liver and the inferior vena cava.

Cases—tabulated.

Name.	Disease.	Age.	Dye Retention after 30 min. %
1. Ernest B.	Normal	26	5
2. John B.	"	29	5
3. Fred E. R.	"	22	10
4. Victor S. M.	"	23	12
5. Doris N.	"	25	20
6. D. Proctor H.	"	27	30
7. Jane B.	"	24	33
8. Marg. H.	"	25	35
9. Fred J.	"	21	45
10. Frank J.	"	26	45
<i>Non-Liver Cases.</i>			
11. Louisa J.	Right hydronephrosis	47	10
12. Louisa P.	Acholic jaundice	26	10
13. Mary R.	Diabetes mellitus after coma	19	10
14. Mrs. W.	Diabetes mellitus	46	20
15. Mrs. S.	Diabetes mellitus	53	35
16. Nellie C.	Parkinsonism	14	10
17. James P.	Cancer of stomach	50	30
18. George S.	Duodenal ulcer	41	Trace
19. Herbert G.	Myopathy of quadriceps femoris	35	4
20. Harry K.	Hyperchlorhydria	21	None
21. Mrs. E.	Mild dyspepsia	61	5
22. John F.	Sciatica	44	None
23. Mary S.	Parkinsonism	36	10
24. John S.	"	51	10
<i>Blood Diseases.</i>			
25. May D.	Hodgkin's disease	30	30
26. Henry H.	Myeloid leukaemia	30	Trace
27. Elsie C.	Anaemia gravis	2	25
28. Mrs. R.	Anaemia (secondary)	29	25
29. Hilda M.	Splenic anaemia (first stage)	9	30
30. John W.	Lymphatic leukaemia	68	15
31. Joseph R.	Splenic anaemia (second stage)	12	15
32. John P.	Pernicious anaemia	52	25
33. Beatrice B.	Myeloid leukaemia	20	20
34. Sarah W.	Lymphatic leukaemia	12	None
<i>Nephritis.</i>			
35. George M.	Acute exacerbation of chronic nephritis	29	10
36. St. V. S.	Chronic inter. nephritis with cardiorenal failure	53	30
<i>Cardiac Cases.</i>			
37. Leonard B.	Aortic disease with cardiac failure	57	5
38. Mrs. A.	Auricular fibrillation, comp.	43	10
39. John E.	" " " "	38	20
40. Florence D.	" " cardiac failure	26	40
41. Mrs. S.	Aortic disease, cardiac failure	33	60
<i>Doubtful Toxaemias of Pregnancy.</i>			
42. Mrs. P.	? Toxaemia of pregnancy	33	40
43. Mrs. P.	? " "	40	35
<i>Obstructive Jaundice.</i>			
44. John E.	Cancer of head of pancreas	35	110
45. Cecil L.	" " " "	29	140
46. Mrs. M.	Ligation of common duct	45	100

Name.	Disease.	Age.	Dye Retention after 30 min.
	<i>Catarrhal Jaundice.</i>		%.
47. May S.	Complete	6	30 *
48. Hughes (f.)	Mild	4	20
49. John T.	Acute hepatitis from suppurating hydatid of liver	30	70
50. Dorothy P.	Mild	9	100
51. George C.	Subacute liver atrophy after N.A.B., jaun- dice clearing	40	20
52. Hilda G.	Subacute atrophy	16	80 (clearing) 10 (convalesc.)
	<i>Atrophic Cirrhosis.</i>		
53. Edward F.	Specific disease, liver large	53	30
54. Mrs. B.	No ascites	44	40
55. Walter S.	Liver large, no ascites	63	60
56. Mrs. O.	Acute exacerbation of disease, slight jaundice and ascites	46	25
57. Harry F.	Had gross ascites, none at test	(?)	12
58. William D.	Arsenical cirrhosis with recurrent ascites	34	22 (3 times)
	<i>Doubtful Cirrhosis.</i>		
59. Herbert B.	Liver pain	52	65
	<i>Mild Acute Cholecystitis.</i>		
60. Samuel M.	Convalescent at time of test	65	10
	<i>Suppurative Pylephlebitis.</i>		
61. Mrs. H.	Slight jaundice	31	40
	<i>Doubtful Cirrhosis (Hanot's)</i>		
62. B. (m.)	Massive hepatomegaly and slight jaundice	37	65
63. Stephen B.	No jaundice at time of test except in conjunctivae	4	5
	<i>Amyloid Disease.</i>		
64. John T.	Large liver and spleen	12	25
	<i>Haemochromatosis.</i>		
65. Fred W.	No ascites	44	20
	<i>Carcinoma of Suprarenal Body.</i>		
66. Hilda A.	Metastases in liver, no jaundice	21	25

I should like to acknowledge my thanks to the Honorary Medical and Surgical Staff of the General Hospital, Birmingham, for their kindness in allowing me access to the cases under their charge, and for much valuable advice; to the kindness of Dr. W. T. Hillier and the staff of the Clinical Pathological Laboratory of the Hospital in giving much time and care to the colorimetric side of the work; and lastly to the Resident Medical Staff for their forbearance in allowing themselves to be tested as the normal controls.

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ON THE EFFECT OF PROTEIN IN THE DIET OF PATIENTS SUFFERING FROM DIABETES MELLITUS¹

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THE problem of the influence of protein in the metabolism of diabetes has been much discussed. Clinicians have noticed that diabetic patients did not do well on diets which contained very large amounts of protein, and this has been attributed both to the effect of the glucose derived from the decomposition of the protein molecule and to a specific dynamic action of protein inducing a higher level of heat production. The problem is complicated by the uncertainty of the origin of the ketone bodies which appear in acidosis. The hypothesis generally accepted is that the production of acetone, aceto-acetic acid, and β -oxybutyric acid depends upon the amounts of total glucose and fatty acids metabolized, and when the ratio of the former to the latter exceeds 1:1.5, ketosis appears.

Recently Petrén (4), from a study of a large number of cases, has produced evidence that acetone excretion runs parallel with nitrogen excretion, and that diabetics show most progress when nitrogen balance is established at a low level of protein metabolism. As a result of his work he maintains that protein metabolism has some inherent deleterious effect on the course of the disease and tends towards the production of acidosis. If Petrén's conclusions are correct, the amount of protein ingested would constitute a decisive factor in dietetic control. As a contribution to the solution of this problem the following investigation was undertaken, with the intention of determining the effect of protein in the diet and the relation of acidosis to protein metabolism. The cases selected for investigation were of moderate severity, and male subjects were chosen in order that the strictest precautions could be observed in the collection of the urine. The diets were carefully controlled, the daily metabolism of protein, carbohydrate, and fat was carefully estimated, and the effect of change in the amount of protein in the diet was studied. The criteria used in estimating response to changes in diet were:

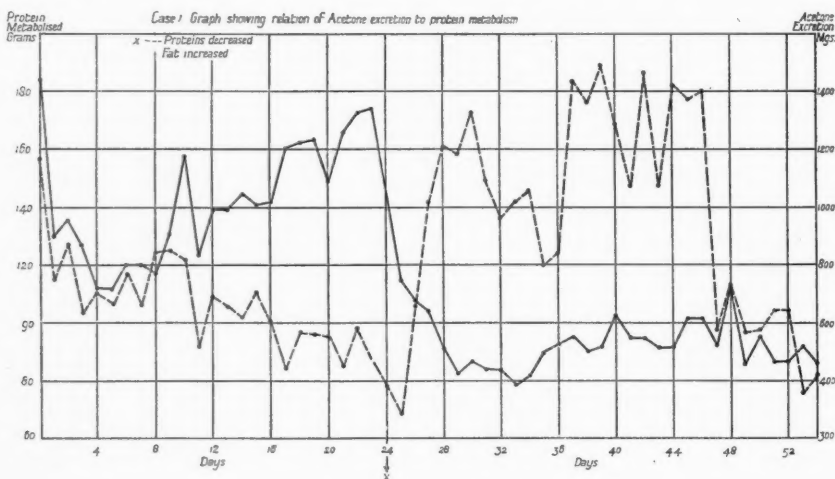
1. Alteration in sugar tolerance and blood-sugar level.
2. Nitrogen excretion and maintenance of nitrogen equilibrium.

¹ Received May 26, 1926.

3. Indices of ketosis: (a) excretion of acetone bodies; (b) ammonia coefficient of the urine; (c) bicarbonate content of the plasma.

The tables of Atwater and Bryant (1) were used for the calculation of food values; Maclean's method (2) was employed for blood-sugar estimation; acetone and aceto-acetic acid were estimated by the distillation method of Messinger and Huppert and total acetone bodies by the method of Van Slyke (3); urinary nitrogen was estimated by Kjeldahl's method, and urinary ammonia by the aeration method of Folin.

Case I. The patient, M. H., was a typical case of diabetes of moderate severity of two years' duration. On admission the fasting blood-sugar value was 181 mg. per 100 c.c. and the urine contained 0.4 per cent. sugar. The patient was given a preliminary diet containing just over 30 calories per kilo, with 68.5 gm. protein, 14 gm. carbohydrate, and 174.5 gm. fat as shown in period I (Table I). The urine became sugar free, but nitrogen equilibrium was



not established, and a week later the protein in the diet was increased to 102.5 gm. to balance the calorie expenditure and to see whether nitrogen equilibrium would be reached. The result was a further rise in the average daily nitrogen excretion, and traces of sugar appeared in the urine. A second increase of protein did not attain nitrogen equilibrium. The patient was now starved for one day and glycosuria ceased. The calorie value of the diet was then increased by the addition of fat, the new diet consisting of 41 gm. protein, 17 gm. carbohydrate, and 196 gm. fat (reduced two days later to 182 gm. fat). The urine remained sugar free, nitrogen balance was not established—the daily nitrogen excretion representing the metabolism of twice the quantity of protein ingested—and the production of acetone bodies was markedly increased (as shown in graph). An addition to the carbohydrate value of the diet slightly lessened the acidosis. A return to a diet with 1 gm. protein per kilo body-weight, 52 gm. carbohydrate, and a moderate quantity of fat, 155 gm., did not appreciably reduce the acidosis, and the excretion of sugar rose as high as 47 gm. in one day, persisting for a week after the reduction of the glucose value of the diet.

This patient thus failed to establish nitrogen equilibrium either with a diet poor in carbohydrate and rich in fat or with a diet containing nearly 2 gm. protein per kilo body-weight. The glucose value of the latter diet exceeded his sugar tolerance, but it is important to note that the actual amount of glucose utilized was greatest during periods II and III, when the protein value of the diet was high, and during this time the acidosis decreased as shown in Table I. On the

TABLE I.
Averages from Protocol of Case I.

Period.	Diet.		Food metabolized.				Urine.		
	P.	C.	P.	Total G.	F.	B. S.	Sugar	Acetone	NH ₃
	gm.		gm.	gm.		%.	Nil.	Mg.	Coefficient.
I (8 days)	68.5	14	121	99	174.5	0.183	0	714	1:13
II (10 days)	102.5	14	139	109	174.8	0.171	Trace	707	1:21
III (9 days)	114.5	14	148	116	174.8	0.186	Trace	494	1:20
IV (9 days)	42	25	85	92	182	0.119	Nil	1112	1:12
V (12 days)	62.5	25	95	80	150	0.180	20	1780	1:11
VI (8 days)	70	39.5	92	108	158.5	0.14	Nil	561	1:16

Insulin units v twice daily during period VI.

other hand, there was a marked increase in the acidosis with the high fat diet of period IV, which only abated when the total glucose metabolized was increased by the action of insulin in the last period. The nitrogen excretion throughout the experiment ran parallel with the ingestion of protein, and during each period a level of nitrogen excretion was reached and maintained. The excretion of nitrogen rose sharply after an increase in the nitrogen of the food, but after a reduction of protein the excretion diminished only gradually. The larger amounts of protein came nearer to establishing nitrogen equilibrium than the smaller. The lowest average nitrogen excretion, i.e. during periods IV and V, was 0.22 gm. per kilo, but there was no nitrogen equilibrium. The sugar tolerance, as judged by the total available glucose metabolized, was highest during periods II and III, when relatively large amounts of protein were being used. If carbohydrate to the sugar value of this protein were actually given the tolerance is immediately overstepped and the excretion of sugar renewed, as in period V, where the total glucose value of the diet was only 8 gm. more than in period III.

Case II. The patient, V. C., aged 22 years, was seen on March 5, 1925. He complained of marked thirst, wasting, and polyuria of a month's duration. He weighed 7 stone 8 lb. The urine contained a large amount of sugar and much acetone, and the blood-sugar was 374 mg. per cent. He was prescribed a basal maintenance diet until his admission to hospital on March 30, when the blood-sugar was 227 mg. per cent. and the urine contained 1.5 per cent. sugar. Starvation was commenced next day and the urine became sugar free two days later, the fasting blood-sugar falling to 113 mg. per cent. The patient was then placed upon a ladder diet, and on May 11 had reached one containing 56 gm. protein, 40 gm. carbohydrate, and 184 gm. fat, the urine still remaining sugar free. Nitrogen equilibrium was approximately established with a slight balance on the positive side, and there was a small increase in acetone production. The total glucose value of the diet was 89 gm., and the dextrose fatty acid ratio 1:2. With this diet the amount of acetone bodies passed was clinically negligible. The patient had gradually increased in weight by 6 lb., and therefore some of the fat ingested had been stored. Under these circumstances it is impossible, even with an estimation of basal metabolic rate, to calculate the exact daily consumption of fat.

The intake of protein was further reduced to 25 gm. daily, and the fat increased isocalorically, with the result that there was a slight rise in the excretion of acetone bodies, which was never greater than 306 mg. daily. The daily excretion of nitrogen fell, touching the lowest point at 3.9 gm. on May 27. The average for the four days, May 23 to 27, was 4.4 gm., representing the metabolism of 27.2 gm. protein, and the patient was practically on nitrogen equilibrium even at this low figure. By May 24 the patient had increased in weight by an additional 2 lb., which explains the absence of ketosis in spite of the high fatty content of the diet. The nitrogen exchange in this case is similar to that in the series of cases of minimum nitrogen exchange reported by Petré (4).

TABLE II.

Date.	Diet.				Protein used.	Total Glucose.	Glucose Excretion.	Glucose used.
	B. S. %.	P.	C.	F.				
21.6.25	—	49	50	135	83.1	111	50.8	60.2
22.6.25	—	—	—	—	83.1	111	50.8	60.2
23.6.25	0.246	—	—	—	86.1	112.9	45.6	67.3
24.6.25	0.201	—	—	—	86.1	112.9	45.6	67.3
25.6.25	0.291	—	—	—	72.1	104.8	66	38.8
26.6.25	0.256	44	17	133.5	72.1	104.8	66	38.8
27.6.25	—	—	—	—	104.1	93.3	47.7	45.6
28.6.25	0.266	—	—	—	104.1	93.3	47.7	45.6
29.6.25	0.266	—	—	—	87.5	80.9	45.8	35.1
30.6.25	0.277	—	—	—	87.5	80.9	45.8	35.1
1.7.25	—	—	—	—	68.7	69.8	30.3	39.5
2.7.25	0.209	—	—	—	68.7	69.8	30.3	39.5
3.7.25	0.213	—	—	—	82.1	77.6	27.5	50.1
4.7.25	0.231	Starve	—	—	82.1	77.6	27.5	50.1

Case III. Part of the record of Case III is shown in Table II. The disease was comparatively severe, the carbohydrate tolerance being only 30 gm. after two days of starvation and then a ladder diet. The record shows an increase in endogenous protein metabolism after the reduction of the diet on 26.6.25. Concurrently there was an increase in the excretion of acetone. Thus in this case alteration in nitrogen metabolism and in the degree of acidosis was consequent upon change in carbohydrate intake.

Case IV. In this patient the urine became sugar free on a diet containing protein 45 gm., carbohydrate 50 gm., and fat 135 gm. (glucose fatty acid ratio 1:1.56). The carbohydrate tolerance was thus 92.3 gm. total glucose. Upon this diet the average daily N. excretion was, for 8 days, 11.5 gm., the average excretion of acetone 404 mg. daily, and the ammonia coefficient 1:21. Later, upon a diet containing P. 36, C. 26, F. 196 (2,012 cal. and G/FA = 1:3), the average N. excretion fell to 7.8 gm., but the output of total acetone bodies rose rapidly to as high as 5 gm. daily, while the ammonia coefficient fell to 1:8.7. The protein was now increased to 64 gm. daily. The result was an increase in N. metabolism to an average of 10.7 gm., but in eight days the excretion of total acetone bodies had fallen to 1.7 gm. daily and the ammonia coefficient returned to 1:22. Upon a return to a diet of G/FA ratio 1:1.8 and 2,090 calories (P. 67.5, C. 45.5, F. 182) the excretion of acetone bodies became negligible.

The results point clearly to the relation of acidosis to the relative amounts of total glucose and fatty acids metabolized. Moreover the change in diet in period III was effected by doubling the ingestion of protein, the other two factors remaining constant, and though nitrogen metabolism was increased, the acidosis decreased markedly.

Case V. The patient, aged 32 years, was seen early in July, 1925, when he complained of loss of weight. Thirst had not been troublesome, but an attack of

sickness and vomiting had caused him to seek medical advice. The blood-sugar was 0.408 per cent., and the urine contained much sugar and acetone. A preliminary diet reduced the fasting blood-sugar to 0.201 per cent. on July 9, and the urine contained 2 per cent. sugar and 40 mg. acetone per 100 c.c. A diet containing 49 gm. P., 50 gm. C., and 135 gm. F., did not materially alter these findings. The excretion of sugar was remarkably steady on this diet, remaining at 22 gm. daily from July 9 to 15, with the exception of one day. The average protein metabolized was 60.7 gm., but equilibrium was not established. The total glucose value of the food ingested varied from 96.2 to 116.5 gm. daily, and the carbohydrate used from all sources remained steady about 75 gm. daily.

A reduction of carbohydrate caused in this case an increase in the endogenous protein metabolism, reaching an average of 73.5 gm. daily for ten days, even though ingested protein was reduced to 36 gm. daily and the fat increased to 196 gm. (calorie value 2,012, 35 calories per kilo).

Discussion.

The factors in protein metabolism to be discussed in the light of the above results are the attainment of nitrogen equilibrium, the tolerance of the patient for glucose, and the production of ketosis.

The attainment of nitrogen equilibrium in the diabetic is recognized to be difficult. Some workers have found it impossible, as in the case of C. K., published by Geyelin and Du Bois (5). Marsh, Newburgh, and Holly (6), however, were able to maintain a low nitrogen equilibrium by administering relatively high fat diets, and Petré (4), although in only thirty of a large series of cases, found that nitrogen balance was reached when the protein metabolized was less than 0.35 gm. per kilo body-weight. 'Indeed', he remarks, 'in health a minimum nitrogen exchange has never been reached without giving the full calorie value necessary for the individual, whereas I have found in a limited number of cases of diabetes that minimal nitrogen exchange was possible, even on a calorific value slightly below the needs of the patient.'

My series of cases do not wholly support this view. Although Case II reached nitrogen balance while metabolizing 56 gm. protein, 40 gm. carbohydrate, and 184 gm. fat, and Case IV almost attained nitrogen equilibrium with P. 64, C. 26, and F. 192 gm., Case I failed to attain nitrogen balance even with 114 gm. protein daily, and in Cases III and V, where the sugar tolerance was low, nitrogen equilibrium was never reached with low protein diets.

The attainment of nitrogen equilibrium depends upon the varying degree of ability to utilize glucose, and, if only a minimal quantity of sugar can be oxidized, the patient is thrown back on endogenous protein and fat as a source of energy. Even in normal individuals on low carbohydrate intake it is difficult to reach nitrogen equilibrium. Kayser, for instance, (7) could not replace carbohydrate in the diet by isodynamic amounts of fat without a rise in the output of nitrogen, and McCann (8) found it possible to maintain nitrogen balance (in tuberculous patients) with 37 to 44 gm. protein daily only when

the diet contained fat and carbohydrate sufficient to make its total calorie value 1.7 to 2.4 times the basal energy requirements.

In view of the difficulty of maintaining nitrogen equilibrium it is perhaps unwise to aim at a very low level of nitrogen balance, unless there are good reasons against allowing more liberal protein metabolism. Very high protein diets are undoubtedly bad, since it is known by experiments on the dextrose-nitrogen ratio in the phloridzinized dog that 58 per cent. of protein, exogenous or endogenous, can be excreted as glucose. This finding has been confirmed in total diabetes in man (Wilder, Boothby, and Beeler (9)). Maclean, however, has shown (10) that the absorption of 250 gm. of meat containing 48 gm. of protein and 27 gm. of available glucose did not, in one case, appreciably raise the blood-sugar during five hours' observation. Nevertheless, long-continued dieting with large quantities of protein will raise the average level of blood-sugar and may renew glycosuria. Thus in Case I of this series an increase of protein to 114 gm. daily resulted in an increase of urinary sugar from 9 to 19 gm. It is, however, interesting to note that the largest amount of total glucose metabolized in this case was during the period of high protein ingested. The protein glucose, becoming only slowly available, is more liable to be utilized, whereas, if the same amount of glucose be given as carbohydrate, the tolerance is immediately overstepped.

Again, the metabolism of protein has been shown to raise the metabolic rate farther than isodynamic amounts of carbohydrate and fat. Boothby and Beeler (11) demonstrated a rise in the metabolic rate of their patients from -20 per cent. to -10 per cent. by a diet containing 103 gm. protein. But this cannot be an extremely important factor with diets containing from 75 to 100 gm. protein daily.

Petrén, however, studied the effect of protein in the diet chiefly with regard to its influence on ketosis. In his opinion the production of ketone bodies is increased by high protein metabolism. '*Dans tous les cas graves du diabète l'organisme est très sensible quant à la quantité d'azote échangée. Cette sensibilité se montre dans des directions différentes, mais pour ce qui est de l'acidose, il faut conclure qu'il y a pour chaque cas grave un certain seuil pour l'azote échangé. Aussitôt que la quantité d'azote échangée dépasse ce niveau, l'acidose apparaît. Mais d'autre part, aussitôt que l'azote échangé tombe au-dessous de ce niveau, l'acidose commence à diminuer et puis à disparaître*' (12). Fasting, he avers, reduces acidosis, since the nitrogen exchange is decreased, and he attributes the occurrence of acidosis in starvation in the normal individual to an increased katabolism of body protein. He agrees with Forssner that days of fat diet alone may increase acidosis.

A study of the records of his cases (13) suggests that the alteration in severity of ketosis is attributable more to change in the ratio of carbohydrate and fat metabolized than to alteration of nitrogen exchange, and that the concurrent amelioration of acidosis and diminution of nitrogen exchange are due to increased sugar tolerance. Where the capacity to use glucose does not

spontaneously improve, acidosis persists and nitrogen balance cannot be reached on account of katabolism of body protein. On the other hand, Case No. 80 in Petré's series affords an instance of decrease in acidosis in spite of high nitrogen metabolism, apparently for the reason that glucose tolerance has improved.

Petrén appears to have been unaware of the work of Woodyatt (14), who, following the researches of Shaffer, developed a formula for constructing a diet balanced as to ketogenic and antiketogenic factors. Shaffer (15) has shown that *in vitro* one molecule of glucose is necessary for the complete combustion of one molecule of fatty acid. (The molecular weight of glucose being 180, and the average molecular weight of the three common fatty acids 256, the ratio in grams of ketogenic to antiketogenic factors in a balanced diet becomes 1.5:1.) The formula of Woodyatt, $F = 2C + \frac{1}{2}P$, satisfies this premiss, for it is the simplification of the equation $\frac{C + 0.58P + 0.1F}{0.46P + 0.9F} = \frac{1}{1.5}$. The antiketogenic value

of the glycerol component of fat has been questioned. McCann and Hannon (16) state that its effect on the respiratory quotient runs parallel with that of glucose in individual cases. Goldblatt, in a personal communication, states that he found that glycerol did not raise the blood-sugar in man or appreciably reduce ketosis, although a reducing substance, possibly glycerol or glyceric aldehyde, was excreted in the urine. Recently, however, Voegtlin *et al.* (17) put forward evidence that glycerol will raise the blood-sugar in fasting rabbits. It is unnecessary to summarize the stages of the proof of the origin of the ketone bodies of acidosis from fat and in lesser degree from protein. An excellent *résumé* of the literature on this subject up to his time is given by Hurtley (18), and recent dietetic and chemical experiments have furnished confirmation of the work of earlier investigators. The experiments presented here are in agreement with the principle that excessive production of ketone bodies can be avoided by preserving a ratio of antiketogenic to ketogenic factors in the diet in the neighbourhood of 1:1.5. The effect of protein has been found to be in accordance with the ratio of glucose and fatty acids derived from it. Thus in Case I a decrease in acidosis was actually produced by an increase in the protein content of the diet, and in this case also the period of highest glucose utilization was during the period of highest protein metabolism.

Conclusions.

1. Nitrogen equilibrium is desirable in the diabetic to prevent loss of body substance.
2. This is possible on low protein diet if carbohydrate and fat can be utilized in sufficient quantities to provide the energy requirements.
3. Very high protein diets are undesirable on account of their power of sugar production and their specific dynamic action.
4. No evidence has been found that protein diets up to 2 gm. per kilo have any deleterious effect on sugar tolerance.

5. Protein has not been found to increase ketosis. This is contrary to the published findings of the Petré school, who state that increased ketosis runs parallel with increased nitrogen excretion.

6. The results obtained are in agreement with the theory of the ketogenic-antiketogenic ratio of Shaffer and Woodyatt.

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LEAD STUDIES. XV. THE EFFECT OF THE PARATHYROID HORMONE ON THE EXCRETION OF LEAD AND OF CALCIUM IN PATIENTS SUFFERING FROM LEAD POISONING¹

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Introduction.

PREVIOUS investigations of the mechanism of lead absorption and excretion (1) indicated that the metabolism of lead was closely allied to that of calcium. Various studies (2), (3), (4), (5), (6), have also established that there is a selective localization of lead in the calcareous portion of the bones, where it is probably stored as the very insoluble tertiary lead phosphate (7). Under normal conditions it may remain inactive for long periods of time, but an alteration towards the acid side of the usual hydrogen-ion concentration of the organism may liberate this stored lead, probably by transforming the tertiary lead phosphate into the much more soluble secondary lead phosphate (8). Thus various observations (1) on both cats and man have shown that the production of an acidosis by the ingestion either of phosphoric acid or of ammonium chloride definitely increases the excretion of lead. This effect is accentuated where a diet deficient in calcium is given. The theory which has been suggested for this is that, because both lead and calcium are held in the body at a common site and as similar chemical compounds, the same physiological conditions would favour the liberation of both. Thus a very deficient intake of calcium, by causing a liberation of reserve stores of calcium salts from the skeleton, also causes an increased liberation of lead. It was further observed that a high calcium diet quickly relieved the toxic episodes of lead poisoning and apparently reduced the excretion of lead. These observations, made in previous investigations in this series, afford the evidence on which is based the theory that lead and calcium metabolism run parallel. The procedures mentioned are in use as improved methods of treatment for promoting the excretion or storage of lead.

When the work of Hanson (9), Berman (10), Collip (11), and Hjort, Robison, and Tendick (12) made available a potent extract of bovine parathyroids, the opportunity occurred for a more direct confirmation of the above hypotheses.

¹ Received May 31, 1926.

The fifteenth of a series of studies on lead poisoning carried out at the Harvard Medical School. For references to the previous articles see *Medicine*, Baltimore, 1925, iv. 1.

[Q. J. M., Jan., 1927.]

Collip showed that his extract, when administered to parathyroidectomized dogs, prevented tetany by restoring to normal the level of the blood-serum calcium (11). He also showed that elevations in the level of blood-serum calcium could be produced in normal dogs, and that successive injections of the extract produced marked hypercalcaemia (13). It was soon proved in cases of parathyroid tetany in man (14), (15), (16), (17) that this extract would raise the blood-serum calcium to the normal level with clinical cure. More recently (18), successive doses in patients with a normal blood-serum calcium have produced hypercalcaemia.

Purpose of Observations.

These facts can obviously be utilized to study the problem of the excretion of lead and of calcium in plumbism. By giving parathyroid extract to patients on a low calcium diet a considerable negative calcium balance might be produced. If at the same time the lead excretion were to be increased, the parallelism between the metabolism of lead and of calcium would be firmly established. Further, if this occurred, it would afford conclusive proof that parathyroid draws calcium from the bones, for practically all the lead is stored there.

In addition to these more fundamental problems, we had the opportunity to investigate the effect of parathyroid extract on the blood chemistry of our patients, and also to contribute to the vexed question of the relation of the parathyroid glands to calcium excretion. This question has been much discussed since the pioneer work of MacCallum and Voegtlin (19). These workers found a reduced calcium content in the blood-serum of dogs after parathyroidectomy, an observation which has since been abundantly confirmed. However, their statement that such dogs showed an increased excretion of calcium has not yet been corroborated. Cooke (20) repeated their work and was unable to find any change in the excretion of calcium after parathyroidectomy. In spite of this contradictory report, the statement of MacCallum and Voegtlin became widely accepted. Thus arose the idea, to which Salvesen (21) later contributed, that parathyroidectomy was associated with a lowered threshold for the excretion of calcium by the intestines. It was supposed that the resulting drain on calcium kept the blood-serum calcium at a low level. Greenwald and Gross (22) have demonstrated that the true conception of the relation of the parathyroid glands to calcium excretion is the very reverse of that above stated. By a technique which eliminated many sources of error incurred in previous animal experiments, they showed that dogs after parathyroidectomy actually showed a *decrease* in the excretion of calcium. In a later series of experiments (23) they were enabled, by the use of Collip's parathyroid extract, to approach the problem from the opposite point of view. They injected normal dogs with the extract, and found that the increased concentration of calcium brought about in the blood-serum was followed by an *increase* in the excretion of calcium. Their contributions to the physiology of the parathyroid glands were published at a time when our investigations were already in progress. Thus independently

we had commenced a study in man which forms an interesting parallel to that of Greenwald and Gross in dogs.

Ward Methods.

The cases chosen for treatment by parathyroid extract were men either with relatively severe chronic lead poisoning or with acute lead poisoning where all toxic episodes had subsided. They were studied in a special ward at the Massachusetts General Hospital, under the charge of a metabolism nurse who had no duties except to see that the necessary régime was carried out. The period of their stay in hospital varied from seven weeks to five months, and during this time all the excreta were collected. The urine was obtained in 24-hour specimens preserved by powdered thymol, the faeces in individual specimens. Since chemical analyses were made of the excreta for three-day periods, 0.3 gm. of carmine alum lake was administered orally in a gelatin capsule every third day, to permit accurate collection of faeces as well as urine. This dye was given at one o'clock in the afternoon, and its first appearance in the faeces marked the end of the period; the collection of urine for this same period ended at nine on the following morning. In order to do away with as many variable factors as possible during medication, the patients were kept at selected intervals on a special diet, in which the daily calcium intake was kept constant at some such low level as 110 mg. or less. During the first few days they were allowed to choose whatever seemed most attractive from the list of foods containing little or no calcium; and thereafter, not only was the daily ration kept strictly uniform, but the patient was given *exactly the same diet* until the next control period began. The patients usually accepted this monotonous diet quite well, and no ill effects of the calcium deficiency became apparent. All food was weighed, and the amount of any which remained uneaten was determined and deducted from the total. A list of the different foods given and the calcium content may be found in a previous publication (1). The hospital water was found to contain 20 mg. of calcium in 6 litres. This was disregarded because, with the small variations of water intake occurring in a three-day period, it could hardly be supposed to introduce a significant variable. Some slight error might have occurred in our earliest investigations owing to the fact that aperients were given without being recorded. Later, all medication such as aromatic extract of cascara and aspirin was analysed for calcium, and the equivalent amount was added to the corresponding record for calcium intake.

Where necessary, the calcium intake was raised either by the addition of calcium lactate to the diet or by allowing the patient to receive the regular hospital diet with extra milk, eggs, and ice-cream. An attempt was made to make long control observations before and after every period of medication, though this sometimes failed because of the difficulty of keeping men in the hospital for a prolonged time.

Laboratory Methods.

The urine and faeces were divided into three-day periods and analysed separately. Quantitative estimations of the amounts of lead excreted were made by Fairhall's method (24), and he kindly helped us in perfecting our technique. Briefly, the method consists in ashing the organic material in an electric muffle furnace at a low heat, precipitating the lead as sulphide from a solution of the ash, re-precipitating the lead as chromate from a solution of the sulphide, and determining the lead present by iodimetric titration. In this determination the chromic acid derived from the lead chromate reacts with an excess of potassium iodide, and the liberated iodine is then titrated against a standard solution of sodium thio-sulphate, starch being used as the indicator.

Since the calcium is present in the excreta in very much larger quantity than the lead, estimations could be made on a twentieth part of the solution of the faecal ash and on a twentieth part of the three-day urinary period, which was ashed separately. The method used was that described by McCrudden (25). Briefly, this consists in precipitating the calcium quantitatively as oxalate. The precipitate is filtered off and washed free from chloride, first with a weak solution of ammonium oxalate, and then with water. It is then suspended in water and treated with sulphuric acid, and the oxalic acid liberated is titrated against potassium permanganate.

The blood calcium was estimated by the Kramer-Tisdall method as modified by Clark and Collip (26). Our blood samples were all taken into sodium citrate, so that our estimations are on the blood-plasma calcium and, therefore, do not compare accurately with those of authors using the blood-serum calcium. However, we subsequently found, in a series of parallel observations, that the plasma calcium by this method bore a close relation to the serum calcium, and the average figure showed it to be 0.7 mg. lower than the serum calcium. Estimations of the phosphorus content of the blood-plasma were made by the method of Briggs (27). The non-protein nitrogen was determined on occasion by the method of Folin and Wu (28), using oxalated whole blood. The carbon dioxide content of the venous blood, in volumes per cent., was determined from time to time by the Van Slyke method (29), using oxalated whole blood taken under liquid paraffin.

Cases treated.

Six patients suffering from lead poisoning were studied. On admission the following investigations were carried out: Complete blood count, blood Wassermann reaction, non-protein nitrogen of the blood, routine urinary examination, and blood-pressure. In the case reports which follow, no mention is made of these findings unless they were abnormal or became so later. The same remark applies to the findings on physical examination.

Case I. M. G. H. 273240. Nicola D., 55, Italian, rubber mixer for seven years.

History. He was employed in the mixing-room of a rubber works where a powder containing oxides of lead was used for vulcanizing. The occupation

was very dusty. For two months he had had attacks of generalized abdominal pain with severe constipation. The pain had persisted every day and was often sufficiently severe to double him up. He had had a similar attack three years before.

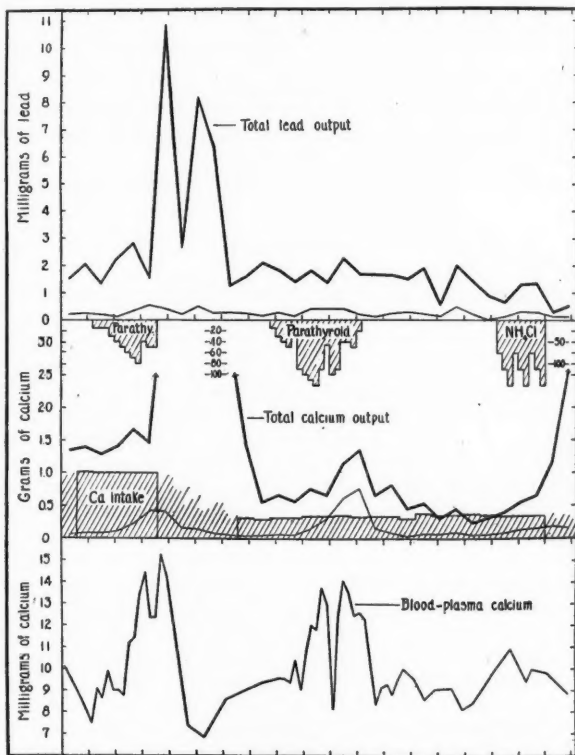


CHART I.

CHARTS I-VI. *The effects of medication and diet upon the excretion of lead and of calcium.*

The interval marks on the abscissa represent five days.

In the upper portion of each chart is shown the lead excretion. The faint line is the excretion of lead in the urine expressed in output for three days. The heavy line is the total excretion of lead in the urine and faeces for three-day periods. Where dotted lines or gaps occur, the corresponding specimens were either incomplete or lost.

In the middle portion of each chart the upper blocks represent medication. In the case of ammonium chloride, the scale indicates cubic centimetres of molar solution per day. Where parathyroid was given, the adjacent scale represents units per day. In the case of thyroxin (vide Chart III), each vertical arrow represents an intravenous dose of 10 mg. The lower blocks represent the calcium intake in three-day periods, and, where the figure exceeds 0.7 gm., calcium lactate had been added to the diet. The areas which have no enclosing block-line represent periods of unweighed high calcium diets. The faint line is the excretion of calcium in the urine expressed in output for three days. The heavy line is the total excretion of calcium in urine and faeces for three-day periods. The distance between heavy line and blocks, therefore, represents the positive or negative calcium balance.

In the lower portion of each chart is shown the blood-plasma calcium.

Exposure to lead last occurred two months before admission.

Examination. He had a sallow appearance and a marked lead line. Occasionally he complained of generalized abdominal pain, but this was not severe. The abdomen was quite flaccid and showed no tenderness.

Laboratory findings. Red cell count 3,120,000 per c.mm. with marked stippling of the cells. Haemoglobin 50 per cent. White cell count 8,200 per c.mm. Polymorphonuclears 60 per cent. Lymphocytes 30 per cent.

Course. After treatment of the constipation and five days on a high calcium intake, all pain ceased. The general condition continued to improve, and, except for a single attack of colic in the eighth week, the symptoms did not recur.

On discharge the lead line was scarcely more than a faint speckling. The red cell count was 4,100,000 per c.mm., and very few stippled cells could be found. Haemoglobin 70 per cent. White cell count 7,500 per c.mm. Polymorphonuclears 73 per cent. Lymphocytes 24 per cent.

The treatment, together with the excretion of lead and calcium, is shown in Chart I.

Case II. M. G. H. 272916. Joseph T. P., 60, Canadian, painter for twenty years.

History. For the past five years he had had repeated attacks of 'painters' colic'. He had had to give up work eighteen months before because of bilateral wrist-drop, which developed gradually, first in the right hand. For three weeks the shoulders had been affected and the disability in his arms had increased so much that he could not raise them sufficiently to feed himself.

Exposure to lead last occurred eighteen months before admission.

Examination. A sallow, emaciated man. He was too weak to stand alone and seemed to be in a precarious condition. There was complete bilateral wrist-drop combined with the upper arm type of paralysis, which was worse on the left side than on the right. Both arms hung flaccid from the shoulders, and voluntary power was completely absent in the left shoulder and practically absent in the right. There was marked weakness and wasting of the deltoids and spinati, worse on the left side, slight weakness and wasting of the triceps, worse on the left side, and some weakness and wasting of the left pectoralis major and right biceps. The extensors of the wrists on each side were wasted and seemed completely paralysed. The flexors of the wrist on each side were unaffected, as were also the small muscles of the hand. No sensory changes could be detected, and elsewhere in the nervous system abnormal physical signs were absent. The upper jaw was edentulous, and the few remaining lower teeth showed severe pyorrhoea with a very marked lead line on the corresponding gums. The peripheral arteries were hard, nodular, and tortuous. The blood-pressure was 140/80.

Laboratory findings. Red cell count 3,530,000 per c.mm. with many stippled cells. Haemoglobin 60 per cent. White cell count 7,900 per c.mm. Polymorphonuclears 79 per cent. Lymphocytes 16 per cent. In the cerebrospinal fluid the Wassermann and colloidal gold tests were negative: no test for lead was carried out.

Course. He developed an ulcerative stomatitis which healed after the remainder of his teeth were extracted. In addition to treatment directed to the elimination of lead, he was given courses of massage and hot air baths. After three months his general condition showed considerable improvement, so that he was able to walk without assistance. In the fourth month great improvement occurred in the power of abduction at the right shoulder, so that he could raise the right arm above the head and ultimately could just feed himself. The muscles of the left shoulder girdle remained very weak, and complete bilateral wrist-drop persisted. In spite of the deficient diet given he gained seventeen pounds during his four months in hospital.

On discharge the red cell count was 3,700,000 per c.mm. and very few stippled cells could be found. The haemoglobin was 60 per cent, and the white cell count 6,400 per c.mm. Polymorphonuclears 75 per cent. Lymphocytes 18 per cent. He was edentulous and the gums were clean.

The treatment, together with the excretion of lead and calcium, is shown in Chart II.

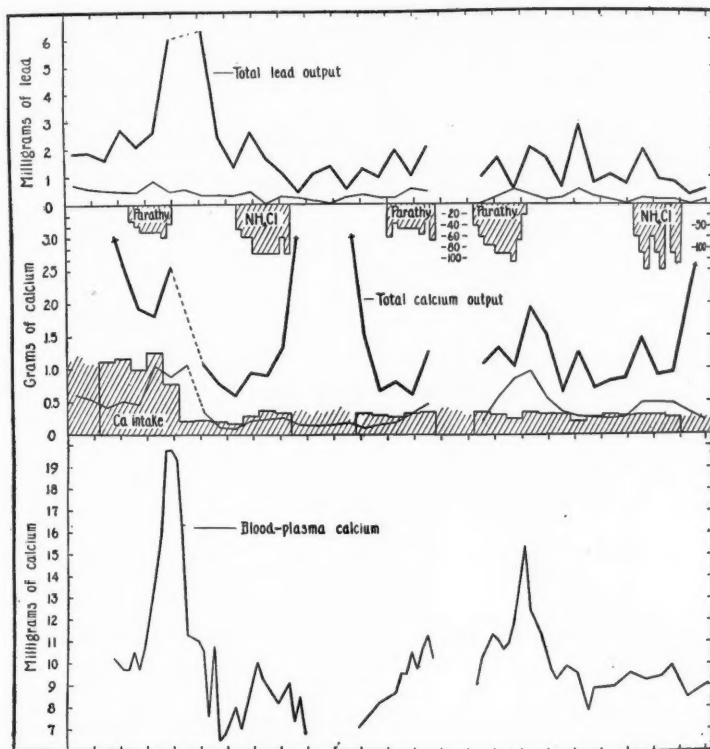


CHART II.

Case III. M. G. H. 271390. Peter S., 39, Russian Pole, painter for twenty years.

History. He first sought advice three years ago for abdominal pain. His doctor found a 'blue line' on his gums and told him he had lead poisoning. Since then he had used paint constantly and was often employed in the dry sand-papering of painted surfaces. Eighteen months ago he noticed weakness of the middle and ring fingers of the right hand. This had rapidly progressed, involving all the fingers and the wrist of that hand. Two months later the left hand had been similarly affected. Since then he had intermittently improved, but was always much worse after taking too much alcohol.

Exposure to lead last occurred two months before admission.

Examination. He was well-nourished, and his colour was fairly good, but he had a distinct lead line. The peripheral arteries were palpable but not thickened. The blood-pressure was 155/95. There was complete wrist-drop on the right side, and the extensors of the left wrist were extremely weak. The supinator longus on each side was unaffected.

Laboratory findings. Red cell count 4,900,000 per c.mm. with occasional stippled cells. Haemoglobin 75 per cent. White cell count 10,400 per c.mm. Polymorphonuclears 49 per cent. Lymphocytes 49 per cent.

Course. In addition to treatment directed to the elimination of lead, he was given courses of massage, and the wrists were supported by splints. After three weeks in hospital he developed a slight tenosynovial effusion on the dorsum of the left hand, but this rapidly disappeared. He gradually regained voluntary power of extension of both wrists, though the right showed less improvement than the left. At the end of five months in hospital he could extend the left wrist fairly powerfully, though the power and range of extension on the right side were still poor.

On discharge the lead line was still present. The red cell count was 5,000,000 per c.mm., and no stippling was found. Haemoglobin 70 per cent. White cell count 5,050 per c.mm. Polymorphonuclears 70 per cent. Lymphocytes 18 per cent.

The treatment, together with the excretion of lead and calcium, is shown in Chart III.

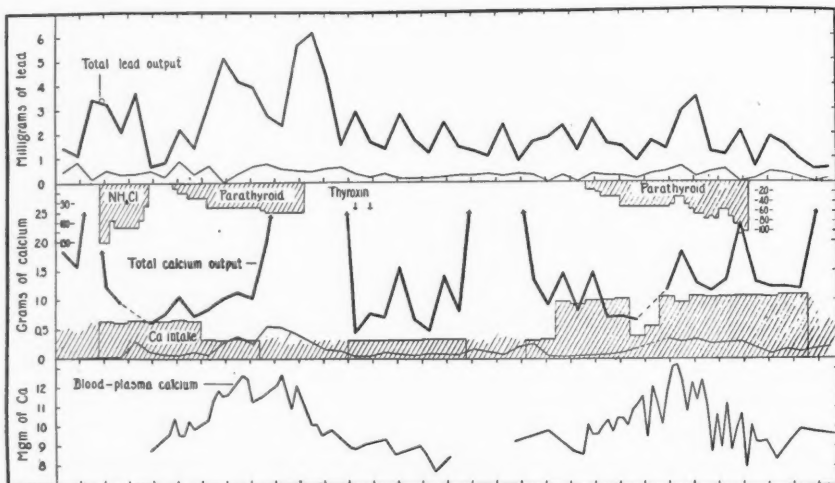


CHART III.

Case IV. M. G. H. 272890. Maico C., 50, Italian, farm hand.

History. He had lived for $2\frac{1}{2}$ months on a farm, where the water came from a well and was contaminated with lead from the exit pipe. The house water was afterwards found to contain 18 mg. of lead per gallon. For three days he had had severe colic, steadily growing worse. He had previously had no symptoms, and he denied all knowledge of lead.

Exposure to lead had continued until the day of admission.

Examination. He was well-nourished but looked very ill. There was considerable pallor of the skin and mucous membranes and a very marked lead line. He was repeatedly doubled up with severe paroxysmal epigastric pain, during which there was marked hyperaesthesia over the praecordium and epigastrium. The abdomen was quite flaccid between attacks, and no deep tenderness nor mass could be discovered.

Laboratory findings. Red cell count 3,240,000 per c.mm. with stippling. Haemoglobin 60 per cent. White cell count 10,650 per c.mm. Polymorphonuclears 82 per cent. Lymphocytes 12 per cent.

Course. The pain was more prolonged than in any other patient we have studied. During the first three weeks in hospital it recurred in severe attacks, commencing in the epigastrium and sometimes radiating to the praecordium. He

continued to look exceedingly ill, often with the facies hippocratica. Acute gastric ulcer and angina pectoris were considered in the differential diagnosis—the electrocardiogram and opaque meal were negative. Temporary relief from the pain could be obtained by intravenous calcium chloride. Unfortunately, he had a distaste for milk and had to be given calcium lactate by mouth. Large doses of atropin sometimes relieved the pain, but he often had to be given morphia. In the fourth week he began to improve rapidly, and on discharge there were no abnormal signs except anaemia and a lead line. The highest red cell count recorded was 3,500,000 per c.mm. Only an occasional stippled cell could be found on discharge. Haemoglobin 70 per cent. White cell count 7,400 per c.mm.

The treatment, together with the excretion of lead and calcium, is shown in Chart IV.

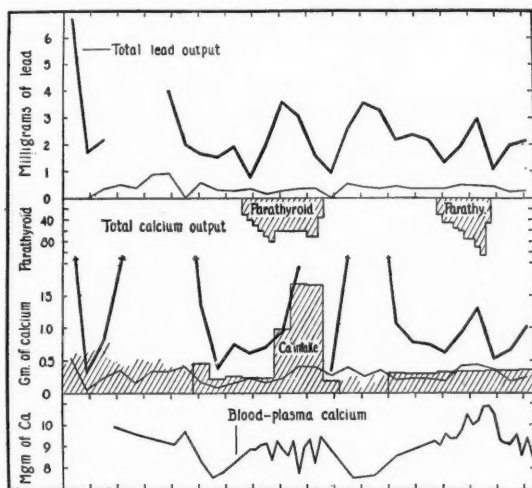


CHART IV.

Case V. M. G. H. 272659. John C., 38, Canadian, painter for twenty years.

History. In the past ten years he had been admitted to five different hospitals for lead colic, and on one occasion had had three attacks of generalized convulsions. A hospital record of five years before showed that he then had a lead line and also marked thickening of the arteries, with a blood-pressure of 175/120. Albumin and casts had been found in the urine. In spite of advice to the contrary, he persistently returned to his occupation. On this occasion, for four days he had had severe generalized abdominal pain.

Exposure to lead last occurred twenty days before admission.

Examination. He looked anxious and ill. Slight pallor of the skin and mucous membranes was present, together with a distinct lead line. The peripheral arteries were much thickened and somewhat tortuous. The blood-pressure was 230/160. The heart was hypertrophied, the apical impulse being seen and felt in the fifth interspace four inches from the mid-line. There was a right wrist-drop as well as slight weakness of the extensors of the left wrist.

Laboratory findings. The urine showed a specific gravity of 1.010, a trace of albumin, and granular casts. The non-protein nitrogen was 60 mg. per 100 c.c. The phenolsulphonephthalein excretion was 35 per cent. in two

hours. Red cell count 3,720,000 per c.mm. with stippling. Haemoglobin 60 per cent. White cell count 12,500 per c.mm.

Course. He was admitted first to the Boston City Hospital, where his distressing abdominal colic was relieved by intravenous calcium chloride. After relief of the colic he was transferred to the Massachusetts General Hospital. He had no further acute symptoms, and the weakness of the wrists gradually improved so that on discharge all movements could be performed, though the extensors of the right wrist remained weak. The blood-pressure on discharge was 160/110. The non-protein nitrogen was on one occasion 75 mg. per 100 c.c., and the phenolsulphonephthalein excretion 18 per cent. in two hours. The lead line could just be detected. Stippled cells were no longer found.

He died at home two months after discharge, apparently from cerebral haemorrhage.

The treatment, together with the excretion of lead and calcium, is shown in Chart V.

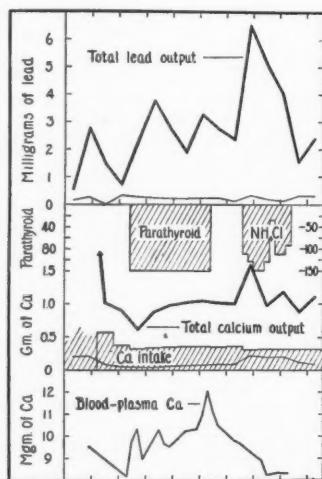


CHART V.

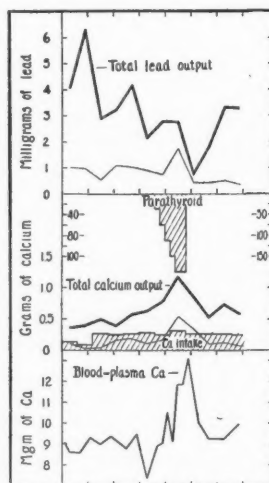


CHART VI.

Case VI. M. G. H. 274439. William L. C., 19, Canadian, mixer in storage battery works for six weeks.

History. There was no history of exposure to lead until six weeks before admission. During that time he had been employed in a small room, weighing out litharge and red lead, which he shovelled into a mixer. The occupation was very dusty, and when he was first seen these oxides could be shaken from his clothes. For the last seven days he had noticed weakness, constipation, and pallor. For four days he had been disabled by severe generalized abdominal cramps which 'felt like tying knots'. Though lessened by aperients, these attacks persisted till admission.

Exposure to lead had continued until four days before admission.

Examination. He was ill-nourished and showed considerable pallor of the skin and mucous membranes. There was a distinct lead line limited to the gum margins of only a few teeth. During attacks of colic the abdomen was of the scaphoid type and showed slight temporary rigidity.

Laboratory findings. Red cell count 3,660,000 per c.mm. Very marked stippling of the red cells. Basophilia. Some poikilocytosis. Rarely a normoblast

was seen, and where it occurred it was always stippled. Haemoglobin 65 per cent. White cell count 6,000 per c.mm. Polymorphonuclears 56 per cent. Lymphocytes 40 per cent.

Course. He had repeated attacks of colic, which were gradually relieved by the use of enemata, aperients, and injections of atropin. After five days the attacks ceased and did not recur, even though he was kept on a low calcium diet. His colour gradually improved, and the lead line practically disappeared.

On discharge the red cell count was 4,104,000 per c.mm. Very few stippled cells could be found. Haemoglobin 80 per cent. White cell count 6,600 per c.mm. Polymorphonuclears 38 per cent. Lymphocytes 49 per cent.

The treatment, together with the excretion of lead and calcium, is shown in Chart VI.

The Effects of Parathyroid Extract on the Blood.

Collip's parathyroid extract was administered to each patient, and in some cases it was repeated after control intervals. The total number of such observations was eleven. The extract was given by intramuscular injection, usually twice a day, though in certain instances it was given three times at intervals of eight hours.

In regulating the dosage we were guided very largely by the level of the blood calcium. In our control observations before treatment we found that, where patients were on a low calcium diet, the blood calcium was often lower than normal, the average figure for all such observations being 8.8 mg. per 100 c.c. This has to be taken into account when elevations of the blood calcium are considered.

In five patients out of six we found that, by giving an average dose of 55 units daily, the blood calcium could be increased to 13 mg. or more within eight or nine days. The most effective method was to give three doses a day and to increase the daily dosage cautiously from, say, 20 to 100 units by adding 10 units daily.

It soon became evident that some individuals reacted more readily than others; for example, in Case II the blood calcium was increased to 19.8 mg. in seven days on an average daily dose of 45 units. The same individual on a later occasion again responded as if he were very susceptible.

In only one individual, however, did the blood calcium show practically no response to the extract. In this man, Case IV, *no rise* in blood calcium occurred after treatment for fifteen days on an average daily dose of 65 units. Later, on the same average dosage, the blood calcium rose only to 10.8 mg. after a period of nine days. It should here be pointed out that this phenomenon by no means indicates an insusceptibility to the effects of parathyroid, for the *total calcium output* in this man was at this time distinctly increased. This is an important observation, for it indicates that the increased calcium excretion is not dependent upon a raised calcium content of the blood.

In nine observations we kept the blood calcium above the normal level for periods of time varying from three days to three weeks. In four of these a mild hypercalcaemia (13 to 15 mg. of calcium per 100 c.c.) was produced and prolonged up to six days without ill effect. In all cases, after cessation of the injections,

the level of the blood calcium rapidly dropped to normal, often within twenty-four hours. During hypercalcaemia no difficulty was ever experienced in obtaining blood from the veins of the arm, and the condition of increased viscosity of the blood observed by Collip (13) in his dogs did not occur. The conditions, of course, were not quite analogous, for we only once produced a rise in the blood calcium as high as that which, when prolonged, proved fatal in Collip's dogs.

Parathyroid caused no significant change in the phosphorus content of the plasma except where considerable hypercalcaemia occurred. Under such conditions readings of 4.5 or even 6 mg. per 100 c.c. were obtained. In Case V, where there was marked renal inefficiency, the phosphorus rose to 6.6 mg. at a time when hypercalcaemia was slight.

In seven of our eleven observations we found a temporary increase in the non-protein nitrogen of the blood when parathyroid was given, the increase being approximately proportional to the dosage. Thus in one case the increase occurred gradually from 30 to 55 mg. per 100 c.c. in two weeks, during which time the daily dosage of parathyroid had been increased from 50 to 90 units. In the case of parathyroid over-dosage, to be described later, it rose as high as 95 mg. per 100 c.c. In all cases it rapidly fell to normal when the parathyroid was discontinued. In no case did symptoms occur, nor was there any abnormality in the urine.

Parathyroid Over-dosage.

Early in our investigations we failed to raise the blood calcium above 12 mg. in three successive patients. We considered the possibility that the low calcium diet might be responsible for this. Four patients were chosen, and parallel series of observations were made on the effect of parathyroid, first when a low calcium diet was given, and secondly when to this same diet were added known amounts of calcium lactate. In Cases III and IV the addition of calcium lactate did not affect the action of parathyroid. In Cases I and II, however, it seemed to facilitate the action of the hormone. Thus, to produce a given rise in the blood calcium, the dosage of parathyroid required was less than half that employed when a low calcium diet alone was given. There are many possible fallacies in these experiments, and we prefer to draw no definite conclusions from them. A recent publication by Collip (17) records similar results obtained from experiments on dogs.

During the above investigations a severe hypercalcaemia was inadvertently produced in Case II. It will be seen from Chart VII that calcium lactate was given for four days before commencing the parathyroid. At this point, owing to an error in the interpretation of the orders, the calcium lactate was reduced and then omitted. During the next two days, the dose was increased to compensate for the previous defects. Meanwhile the parathyroid had been continued in increasing doses, until on the eleventh day the level of the blood calcium had risen to 19.8 mg. per 100 c.c. It remained at this level for forty-

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eight hours; then, although all treatment had been discontinued, it fell only very gradually to normal levels during the next three days.

A very considerable rise in the blood-plasma phosphorus was observed, though coming later than that of the calcium. The highest reading was 6 mg. per 100 c.c., and this occurred twenty-four hours after the maximum rise in calcium. The pH of the blood was not estimated. Dr. J. S. Lawrence found the carbon dioxide content of the venous blood to be 75 volumes per cent. Dr. J. L. Gamble very kindly estimated the total base, protein, and water-content of the serum and found them quite normal (fixed base 158 c.c. N/10 per 100 c.c. serum; water-content 92.2 gm.; protein 5.9 gm.). He also repeated our measurements of calcium and phosphorus, obtaining substantially the same figures on the serum as we had done on the plasma (calcium 19 mg.; phosphorus 5.2 mg.).

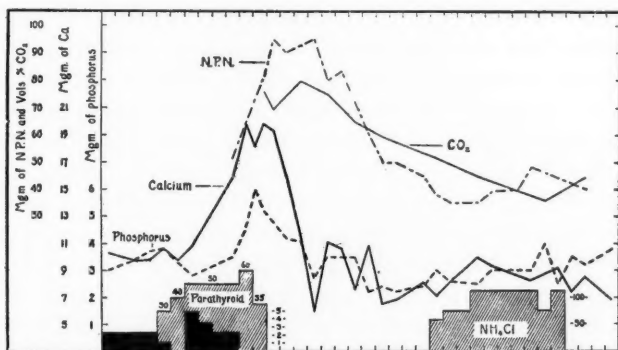


CHART VII. *The effects of parathyroid over-dosage on the chemistry of the blood in Case II.*

The interval marks on the abscissa represent days.

The calcium and phosphorus were estimated in blood-plasma, the non-protein nitrogen and carbon dioxide content in venous blood. A low calcium diet was given throughout (*vide* Chart II). The scale for ammonium chloride indicates cubic centimetres of a molar solution, that for parathyroid units per diem. The black area represents calcium lactate in grammes.

The non-protein nitrogen was followed from the time the serum calcium was first found to be raised. It showed a rise to a maximum of 95 mg. per 100 c.c., this rise occurring two days after the maximum rise in calcium. During the next week it fell gradually to within normal limits.

The changes in the physical properties of the blood observed by Collip (13) in dogs suffering from parathyroid over-dosage were absent, and we never experienced the slightest difficulty in separating the plasma by centrifuge.

Throughout the whole time the patient remained up and about, and, except for slight nausea and loss of appetite, appeared to be normal. The symptoms of hypercalcaemia seen by Collip in his dogs were 'anorexia, vomiting, diarrhoea, weakness, apathy, drowsiness verging into coma, and a failing circulation'.

Effects of Parathyroid Extract on Calcium Excretion.

During our investigations we were able to make nine observations on the effects of parathyroid on calcium excretion when the intake was known. It will be seen from the charts that during control periods on a low calcium diet a negative calcium balance already existed, the average excess of output over intake being 0.37 grm. in a three-day period.

In all our observations parathyroid definitely increased this negative calcium balance to an average figure of 0.56 grm. in a three-day period. This represents an increase of 53 per cent. in calcium output as an average for all doses of parathyroid given. The increase was roughly proportional to the dosage given. Thus in Case I, where parathyroid was given in increasing doses for sixteen days, the negative calcium balance rose to a maximum of 1.01 grm. in a three-day period, a figure very much higher than the average quoted above. When the parathyroid was discontinued, the calcium output did not immediately drop to normal, but remained somewhat raised for periods of from three to six days.

The increase of calcium output was relatively more marked in the urine than in the faeces. An average of all readings shows that parathyroid produced an 83 per cent. increase in the urinary output and only a 20 per cent. increase in the faecal output. Where large doses of parathyroid were given, the urinary output of calcium rose to very high figures. Thus in Case I, where parathyroid was given in increasing doses for sixteen days, the output of calcium in the urine rose from 0.069 grm. to 0.754 grm. in a three-day period.

The relationship between the level of the blood calcium and the calcium excretion is important. Although we found that hypercalcaemia was always associated with an increased calcium output, the converse was not found to be true. In this connexion it may be well to emphasize again the findings in Case IV. In this patient large doses of parathyroid failed to produce a significant rise in the blood calcium, but, in spite of this, the total calcium excretion was doubled.

In considering the physiological action of the parathyroids, the source of such large amounts of calcium appearing in the excreta is of fundamental importance. We consider it justifiable to infer from our results, as Greenwald (23) did from his animal experiments, that the parathyroid hormone causes increased excretion of calcium salts *from the bones*. This will be referred to again when the effects on lead excretion are discussed.

Effects of Parathyroid Extract on Lead Excretion.

Any statement of the effects of parathyroid on lead excretion must take into consideration the time which has elapsed since exposure and the treatment which has gone before. Thus the effects of the *first* administration of parathyroid are strikingly different from those found when it was given a second time to the same patient. For these reasons the results obtained will be considered separately.

When parathyroid was first given, all six of our patients showed increased excretion of lead. This appeared within about six days of the first dose, and usually increased to a maximum about six days *after* the injections of parathyroid ceased. This maximum point was often as high as 6 mg. for a three-day period. In Case I, 10.8 mg. of lead were excreted in the period immediately following the last doses of parathyroid, and values as high as 6.3 and 8.1 mg. followed this. These effects are far greater than those obtained in our previous investigations (1) by the use of phosphoric acid and ammonium chloride.

Close study of the charts shows many points of similarity between the behaviour of calcium and of lead. Thus every increase in lead excretion referred to above corresponds to an increased output of calcium previously described. It therefore follows that, where hypercalcaemia occurred, it was found to bear a definite relationship to the increased excretion of lead. The further observation was made that, after the parathyroid was discontinued and the blood calcium had dropped to normal, this high output of lead often persisted up to three, six, or nine days longer. This was no doubt the period of time necessary for its complete excretion, and corresponds to a similar, though somewhat shorter, period observed in the case of calcium excretion.

In Case IV, where parathyroid produced no significant rise in the blood calcium, there was nevertheless a definite increase in the output of lead, which synchronized with that of calcium already discussed.

The interesting fact about the excretion of lead is that in cases where a large output of lead occurred when parathyroid was first given, repetition of this treatment produced very little effect. For example, in Case I very large doses of parathyroid were used the second time, but almost without effect on the output of lead. The effect produced on the calcium, however, is an exact replica of what occurred before, namely, a hypercalcaemia associated with increased calcium excretion. In all the other cases there was similar evidence that the parathyroid was acting on the calcium metabolism exactly as before. Then why was the output of lead unaffected? Had it become inaccessible, altered in some way, or exhausted from the skeletal deposits?

By analogy with experiments on cats (30) it is unlikely that an excretion of lead measurable in milligrams could exhaust the deposits in the skeleton. Also it has been calculated from analyses of autopsy material (6) that the deposit of lead accumulated in the skeleton of a worker exposed in a lead industry may amount to half a gramme or more. From control observations we know that our patients continued to excrete small amounts of lead long after treatment had ceased, so that lead must have been present in the bones in *some* form throughout our observations. We decided that treatment by ammonium chloride might throw further light on the problem. The effect of its administration on the output of lead in Cases I and II was found to be *less* than that of the second treatment by parathyroid. This suggests that there was no further lead present in a form readily available for mobilization. It should here be pointed out that our observations (1) on the effects of phosphoric acid and ammonium chloride

demonstrated a similar phenomenon, for as time went on it was found progressively more difficult to increase the excretion of lead.

The most satisfactory explanation of our results is that the first administration of parathyroid almost completely exhausts the bones of a certain readily available portion of the lead stored there. This may possibly be lead acquired in the most recent exposure to a source of poisoning. The remaining lead is much less rapidly mobilized, and possibly represents that acquired and stored at some much earlier exposure, even years before. This is excreted gradually in the usual routine of metabolism and is relatively unaffected by the measures of treatment adopted.

These observations indicate why it is so rare to find toxic episodes appearing long after exposure to lead has ceased.

Excretion of Lead during and after Colic.

In two of our cases we had the opportunity to study the amount of lead excreted during and immediately after colic. Case IV was unique in that colic persisted for three weeks after admission. During this time large amounts of lead were excreted, and the curve of total output (Chart IV) continues to drop steadily for thirty-three days. However, a consideration of the case will suggest a fallacy, from the fact that ingestion of lead from the house water-supply was the source of poisoning. Thus the first point on the curve undoubtedly represents to a large extent ingested lead.

However, Case VI is free from this fallacy. Here poisoning occurred by inhalation of oxides of lead, and therefore the total output represents a true excretion. Chart VI shows how for eighteen days the curve of total lead excretion maintains a steady downward trend, ultimately reaching a level about half as high as the original one. It will be noticed that this lower level of excretion resembles closely that found in untreated cases, for example Case II.

Thus in two cases recently exposed to a serious hazard of lead poisoning we find that acute toxic symptoms are associated with a high output of lead. Subsequently this output falls to levels commonly found in cases also recently exposed to a source of lead but showing only chronic manifestations.

The Therapeutic Significance of Parathyroid Extract in Lead Poisoning.

The administration of parathyroid extract has proved a more efficient and more rapid means of increasing the elimination of lead than the methods previously described. Although large amounts of lead are mobilized in the process, none of our patients suffered any ill effects. Its use is, of course, restricted by the fact that repeated determination of the blood calcium is an essential precaution. We are aware that the rise in the non-protein nitrogen of the blood occurring with large doses may mean a direct renal involvement, though this is not the only interpretation. It cannot replace ammonium

chloride in the out-patient clinic, but where a rapid elimination of stored lead is desirable the patient may be admitted to a ward and treated with parathyroid. Used in selected cases, with full appreciation of its possible dangers and with adequate laboratory control, it should prove a useful adjunct to the therapeutics of lead poisoning.

Conclusions.

Collip's *parathyroid extract* administered to six patients with lead poisoning caused considerable excretion of calcium and of lead from the bones.

In most cases the extract caused marked elevation in the blood calcium, though considerable individual variation was found, and one patient showed no significant rise even with very large doses. This effect was observed even on a diet very deficient in calcium. When calcium lactate was added to such a diet, the action of the parathyroid extract was in some cases very much accentuated. Parathyroid over-dosage occurred in one patient. The blood calcium rose to 19.8 mg. per 100 c.c. He complained of nothing more than slight nausea and anorexia.

The increase in calcium excretion occurred irrespective of whether the blood calcium was raised, and it was much more marked in the urine than in the faeces.

Parathyroid extract definitely increased the excretion of lead *when first given*. The amounts excreted were far greater than those obtained in our previous investigations, when ammonium chloride or phosphoric acid were given. When parathyroid extract was *given a second time*, little or no increase in lead excretion was observed, though the extract was known to be potent because it produced its characteristic effects on calcium metabolism.

Evidence is adduced in support of a theory that parathyroid extract rapidly and effectively mobilizes from the bones a certain amount of stored lead which is readily available. The remaining lead is mobilized much more slowly in the usual routine of metabolism. The action of parathyroid extract confirms the theory previously stated, that there is *a very striking parallelism between the storage and excretion of calcium and of lead*.

The rapid elimination of large amounts of lead produced no ill effect. However, owing to the risk of hypercalcaemia and possibly of renal damage, parathyroid extract should be used only in selected cases and always with adequate laboratory control.

We wish to express our deep gratitude to Miss Marian Ropes and Dr. Clark W. Heath for their invaluable help in estimating the urine and faeces for calcium and the blood for calcium and phosphorus in all our patients. We are indebted to Misses Helen Tracy, E. M. Blackburn, and Constance Fulton for technical aid in nursing and dietetics. The courtesy of Eli Lilly and Company of Indianapolis in presenting us with very generous supplies of Collip's parathyroid extract under the trade name 'Parathormone' is duly acknowledged and appreciated.

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THE EFFECT ON BREATHLESS SUBJECTS OF RESIDENCE IN AN OXYGEN CHAMBER¹

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With Plates 1-3

Introduction.

IN two previous papers the effect of exercise on the pulmonary ventilation and respiratory metabolism of certain male breathless subjects has been discussed (1, 2). Our main object was to see what change, if any, was produced in such patients by residence in an atmosphere containing an increased percentage of oxygen, and, further, to find out how long such changes persisted after treatment. Certain details as to the construction of the oxygen chamber used for this purpose are given in the Appendix, with analyses of the contained air. The percentage of oxygen usually varied between 35 and 50 throughout the twenty-four hours.

The method used for investigating the effect of the treatment was the same as that already described in the previous papers. Observations were made before the patients went into the chamber, during their period of treatment, and for some days subsequently, and a complete observation consisted in determining the pulmonary ventilation, rate and depth of breathing, pulse-rate, and metabolism, before exercise, during exercise, and during the subsequent rest period.

As we wished to find out the duration of the changes subsequent to oxygen treatment, none of the observations were made in the oxygen chamber. On each occasion while under treatment they left the chamber and were wheeled across to the laboratory, where they rested until we were ready to test the response to exercise. Thus the time which had elapsed since they left the chamber might be anything between half an hour and three hours when all the three subjects were carrying out the exercise on the same day. The great

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majority of the observations were begun at 10 a.m., after the subjects had had a light breakfast about 8 a.m. Similar investigations were made during the weeks following treatment in the chamber.

One reason for not investigating the changes while the patients were actually breathing an oxygen-enriched atmosphere was that such work had already been carried out. One of the earlier papers which describes the results in a large number of different conditions, and among them breathless patients, is by Beddard and Pembrey (3), who found the pulmonary ventilation and sometimes the rate of breathing much reduced. Some results have also been published by us with the late Dr. G. H. Hunt (4).

Beddard and Pembrey (3) investigated the pulmonary ventilation in patients with breathlessness due to various causes and in some of them observed the effect of breathing oxygen. In patients (*a*) with capillary bronchitis, and (*b*) with cardiac failure due to mitral stenosis or to chronic bronchitis, breathing oxygen constantly diminished the ventilation, sometimes to a considerable extent (about 30 per cent.); the rate, which was frequently very rapid, i.e. 30-50, was much less affected, so that the depth of breathing was actually decreased, except in capillary bronchitis, where the rate was often greatly reduced. In one patient breathing oxygen increased the percentage of carbon dioxide in the expired air from 2.6 to 3.1. They connect this mainly with the diminished ventilation and suggest that the rapid rate was of value in helping the circulation, invoking the principle of the respiratory pump.

Campbell, Hunt, and Poulton (4) investigated the respiration of certain patients, in the first place breathing the ordinary atmosphere, and immediately afterwards either pure oxygen or an atmosphere enriched with oxygen. On four out of five occasions in a patient with valvular disease the pulmonary ventilation was diminished when breathing oxygen. Considerable diminution was noticed in three out of four cases of chronic pulmonary disease, but no change was observed in a case of congenital heart disease. Average values are given in Table I. The rate of breathing was not much changed by oxygen, but the depth was considerably diminished, and, as the carbon dioxide percentage remained much the same, the total carbon dioxide output was diminished when oxygen was breathed.

The present work, so far as residence in the oxygen chamber was concerned, was begun along very much the same lines as those adopted by Dr. G. H. Hunt and others at Cambridge, when he investigated the effect of oxygen on gassed patients (5). In our first series of observations three patients, B., S., and P., lived in the chamber from March 19 to March 24, 1923. In the second series B. and two other patients, W. and H., lived in the chamber from June 6 to June 10, 1923. In the third series another group of three patients, C., G., and M., lived in the chamber from midday on March 3, 1924, after the respiratory observations of that date had been made, until the evening of March 9. They then returned to the ward, but were again admitted to the oxygen chamber on March 24. C. and M. lived in it until the evening of March 29, while G. came

out on the evening of March 26. The patients did not remain the whole of the time in the chamber, coming out each day from 8 a.m. to 9.30 a.m., from 11.45 a.m. to 12.15 p.m., and from 6 p.m. to 7 p.m., for breakfast, dinner, and tea.

TABLE I.

Effect of Breathing Oxygen on the Respiration in Various Diseases.

Disease.		Ventilation. Litres.	Rate.	Depth. c.c.	Carbon Dioxide. Percentage.	Carbon Dioxide. c.c. per Minute.
Valvular disease of the heart (1 patient)	With air	15.1	43	354	1.32	156
	With oxygen	10.9	38	288	1.47	134
Pulmonary disease (4 patients)	With air	7.7	24	301	2.38	125.6*
	With oxygen	6.1	24	206	2.53	85.5*
Congenital disease of the heart (1 patient)	With air	9.8	14.5	676	1.64	139
	With oxygen	9.7	15	646	1.72	145

The oxygen was usually 100 per cent., but sometimes 40 per cent.

* Carbon dioxide results were obtained for two of the patients only. One of them (Case 42) died shortly afterwards, and gave a very low figure.

TABLE II.

Condition of Patient before Treatment.

Name.	Age.	Weight. Kg.	Height. Cm.	Stem Length. Inches.	Chest (Ex- piration). Inches.	Expansion. Inches.	Blood Pressure.	Haemoglobin. Percentage.	Usual Pulse- Rate Range at Rest.
S.	50	76.5	69.5	35.75	37	1	$\frac{103}{80}$	106	68-74
P.	58	74.5	64.7	32	36.3	1 $\frac{1}{4}$	$\frac{135}{88}$	105	70-76
B.	57	79	66	35	35	2 $\frac{1}{4}$ *	$\frac{135}{93}$	96	62-76
H.	47	68	68.5	35.75	35.5	1 $\frac{1}{4}$	—	—	60-70
W.	54	64	72.0	35	35	1 $\frac{3}{4}$	—	—	72-90
C.	60	66	—	30.5	37.5	$\frac{1}{2}$	$\frac{130}{80}$	76	70-86
G.	36	58	69.7	34	35.8	2*	$\frac{115}{88}$	80	90-100
M.	66	76	66.0	35	37.8	1 $\frac{1}{4}$ *	$\frac{135}{90}$	102	60-72

* No change observed after treatment.

Clinical Condition of the Patients. (See also Table II and Plate 3, Fig. 7.)

The vital capacities have already been given at the end of our first paper (1).

S. This patient (aged 50) has already been described (4, Case 29). He began having attacks of bronchitis and asthma in Gallipoli, and since then, in spite of almost constant treatment, he had remained much the same and had always been short of breath even on slight exertion. He was of good physique, with a florid

complexion and distended venules. He was dyspnoeic at rest, but, as judged by the distress produced by the exercise, he seemed clinically to be the least ill of the patients with bronchitis. In 1923 there were râles and rhonchi all over his chest at all times when he was examined. There was always a considerable amount of expectoration—about half a cupful a day. His heart was enlarged about $4\frac{1}{2}$ in. from the mid-line; there were no bruits. His urine contained no albumin.

Treatment in the oxygen chamber seemed to make little if any difference clinically to the patient, and his condition was not much changed when he was examined in 1926. Comment will be made on his bad teeth.

P., aged 58, a labourer who had been a sailor for many years, was admitted under Dr. Hurst on February 16, 1923. The dyspnoea and tightness in the chest had come on acutely two days previously, while working in a hot atmosphere. He had not had any acute attacks before. The diagnosis was chronic bronchitis and emphysema and acute bronchitis with heart failure.

On admission there was cyanosis, visible venous pulsation in the neck, a palpable tender liver and albuminuria. His chest was full of râles and rhonchi and he had frothy sputum. His heart was enlarged 5 in. from the mid-sternal line; his pulse-rate was 92; there were extra-systoles but no murmurs.

A month later, when he was examined before oxygen treatment, all signs of cardiac failure had disappeared, but his chest expansion was poor and there were still signs of chronic bronchitis. The pulse-rate was then between 72 and 78 with a few extra-systoles included.

In this patient it is specially difficult to decide how much of the improvement was due to the treatment in the oxygen chamber and how much to his general recovery from the attack of cardiac failure. He himself said he was at once better for his stay in the chamber and that his cough was better and his sputum not so thick. When seen in 1926 he did not complain of breathlessness, but still had a little cough. He was surprisingly fit and attributed the change to the oxygen chamber. He had been regularly at work as a pipe-fitter for eighteen months in the open air, but had not returned to the hot atmosphere which apparently brought on the previous attack.

B., aged 57, was admitted under Dr. Poulton on February 26, 1923. He had had for fifteen years a winter cough, which had been worse since June 1922, shortly after he became a fur dresser; he had had attacks of breathlessness and orthopnoea with much sputum since November. Diagnosis, acute on chronic bronchitis and right-sided failure. His face was congested, but there was no cyanosis; there was slight dyspnoea at rest on March 3, but none on March 20. He was in the oxygen chamber from March 19 to 24, 1923. There was no albumin or oedema, but slight clubbing of the fingers. On March 3 sibilant rhonchi were present all over the chest, but on the 20th only a few scattered rhonchi. After treatment his cough was less and he felt better in himself. Breath held 17 secs. after normal expiration.

In June 1923, before the second series, he felt better and less short of breath, but still complained of dyspnoea with tightness across the chest and expectoration all day. Rhonchi were heard at the end of inspiration all over the chest. Breath held 12 secs. Twenty-four hours after leaving the oxygen chamber he felt less short of breath and his cough was much better; there was much less sputum, but rhonchi were little changed. Breath held 19 secs.

In August 1925 he thought that the favourable effect of the oxygen chamber had lasted a few weeks. He had not again been so bad as when he went into the oxygen chamber first of all; was able to do light work.

W., a bricklayer, aged 54, admitted under Dr. Poulton on June 4, 1923, had been a healthy man except for bad attacks of eczema during the War. He

had been a heavy smoker, 1 oz. of tobacco a day. In March 1922 he had an attack of extreme shortness of breath aggravated by exercise, diagnosed as asthma. This had continued off and on since, and he had lost about 2 stone. He also had attacks of breathlessness at night.

June 5. Apex-beat just inside mid-clavicular line. Some extra-systoles, no murmurs. Slight general cyanosis. Rhonchi all over chest and some râles. Sputum considerable. No oedema. Urine normal. Admitted into oxygen chamber from June 5 to June 9, 1923. He said his cough and shortness of breath were better in the chamber and improved still more on coming out.

August 1925. Favourable effect of oxygen had lasted three weeks. Then weather became hot and breathing difficult. Prefers winter to summer, but is upset by cold winds. On the whole has been better than in the acute attack when he first came into hospital, but varies very much from time to time and is often hardly able to walk about at all. When seen again, in March 1926, he was out of breath, even when talking, and extremely so as soon as he took any exercise.

H., a blacksmith, aged 47, was admitted under Dr. Poulton, May 14, 1923, with diagnosis of effort syndrome. He had good health up till 1914, when he joined the army, but had myalgia in 1915 and 1916 and was discharged for haemoptysis and supposed valvular disease of the heart in 1917. In 1919 he again had heart trouble, dizziness, and momentary fainting attacks. In June 1923 he complained of breathlessness and pain and was able to undertake only the lightest work. He was very nervous.

The width of his heart orthodiagraphically was 5 in. There were no murmurs or cyanosis or oedema. He had extreme dyspnoea on exertion, and a little sputum in the morning. Breath held 26 secs. His chest was normal, but a soft, low-pitched rhonchus was heard on one occasion. On June 11, 1923, after treatment he felt somewhat better, more free in his chest, but no great improvement. There were no physical signs in his chest. Breath held 26 secs. This improvement lasted for a few days and he then felt as before.

In August 1925 he said he had at times been better as regards his breathing, but had had later a cough and shortness of breath. We have diagnosed this case as effort syndrome, because there was extremely little evidence of bronchitis. His pulse was not unduly rapid.

C., a man aged 60, was admitted under Dr. Poulton on February 19, 1924, diagnosed chronic bronchitis and emphysema. He had had pneumonia at 16, and since then there had been a tendency to cough. Ten years ago he had a bad attack of bronchitis, and since then his condition, especially in the winter time, had been steadily getting worse. He gave a positive test with S. Van Leeuwen's human dandruff extract (8), and a history of sudden breathless attacks suggested that he was primarily a case of asthma.

On March 4 sibilant and sonorous rhonchi all over chest. Expiration prolonged, not marked at rest, severe on exertion. His coughing often prevented him wearing the mask continuously; this improved. He was a good subject, trying to carry out instructions and willing to put up with a good deal of breathlessness. Slight cyanosis of lips and tongue. Heart width (orthodiagraph) $5\frac{1}{2}$ in. No murmurs. No albuminuria or oedema. Breath held 24 secs.

On April 8 subjectively he had obtained great benefit from the oxygen chamber; his cough was less troublesome. Rhonchi still present in chest. He seemed to do the exercise more easily than before, but on the second occasion the effect of the oxygen chamber was not so striking.

Blood (examined by Dr. Howell): February 29, Hb. 76 per cent, R. B. C. 5.3 millions per c.c.; March 10, Hb. 100, R. B. C. 5.1; March 20, Hb. 88, R. B. C. 5.1; resting pulse before oxygen 90-100, after 80-90. Respiration rate before oxygen over 30, after 22-4.

Writing on April 25, 1924, he said he still felt relieved, though cough was still troublesome.

G., a relieving officer, aged 36, was admitted, on February 5, 1924, under Dr. French. Malaria in 1919, accompanied by a most troublesome cough. Following influenza eighteen months ago he began to be short of breath with exercise. It came on insidiously and became continuous. Van Leeuwen's human dandruff test was negative (8). Had coughed up tough pink substance (? fibrin). Breath held 11 secs.

March 3, 1924, diagnosis chronic bronchitis and asthma. Rhonchi all over. He was breathless on talking, but there was no cyanosis. His condition was variable, associated with variation in sensation of tightness. Radiogram showed enlarged root shadows suggestive of chronic tuberculous infiltration. Width of heart (orthodiagraphically) $4\frac{1}{2}$ in. No murmurs. Urine normal. No oedema.

March 10, after first oxygen period, felt better generally and could breathe with less difficulty; the phlegm seemed less sticky and he could cough it up more easily; felt tight at 9 p.m. and chest expansion was only $1\frac{1}{4}$ in.

April 3, 1924, after second period he left better, and found his cough easier while he was in the chamber than immediately after he came out. In spite of this there was not much difference in the ease with which he did the exercise.

Blood examined (Dr. Howell): Feb. 29, Hb. 80, R. B. C. 4.8; March 10, Hb. 98, R. B. C. 5.1; March 20, Hb. 90, R. B. C. 4.9.

He died two years later, but unfortunately the exact cause of death is not known.

M., aged 66, was admitted for breathlessness and praecordial pain on February 25, 1924. He had always had good health till April 1922, when he had to go into hospital for a time. He returned to his work as a carpenter, continuing under medical treatment, but had to give up work finally in July 1923 for breathlessness and pains in the legs. He felt much better when he was discharged, but was not able to go back to work. On readmission he further complained of orthopnoea and short acute attacks of breathlessness at night; also of giddiness, insomnia, and loss of weight. He had attacks of pain brought on by exertion—the pain being substernal and praecordial and a little down both arms—especially if he walked after meals. He was diagnosed as myocardial disease.

His heart was enlarged, both to the right and to the left, the maximum transverse diameter being $7\frac{1}{4}$ in. There were occasional extra-systoles but no bruits. There was a little oedema of his feet on admission, but none when he went into the oxygen chamber; there was no albuminuria. There were no abnormal physical signs in his chest and there was little sputum, although he had a cough. Breath held 15 secs.

He felt better during and after the oxygen chamber on both occasions, March 1924, and always stated that the exercise did him good, but objectively there was not much change. When seen two years later he had not been able to return to work because of the shortness of breath, and was not even able to use his carpentering tools at home for the same reason. But so long as he took things easily he felt fairly comfortable and had fewer attacks of pain. Probably all that can be said is that he was no worse. He was always optimistic about himself and felt that treatment did him good.

In the first series of observations the pulmonary ventilation, depth and rate of breathing, pulse-rate, and oxygen intake were all recorded. The exercise was twelve steps for one minute, the height of the step being 13 in. In the second and third series of observations the carbon dioxide percentage in the expired air was also determined, so that the carbon dioxide output could be

calculated. The exercise used for the second series was eighteen steps a minute for 3 minutes. The patients of the third series were very breathless. One of them, G., could only take four steps a minute for three minutes, while the other two, C. and M., took six steps a minute for three minutes. In this series an intermediate step was provided, as stepping up 13 in. was too much of an effort for these patients. Since the observations in the third series were much more numerous and more complete than in the others, they will be considered first in each section of the paper.

Percentage of Carbon Dioxide in the Expired Air.

One result at once became obvious without any elaborate analysis of the figures, and will therefore be taken first. In all three subjects in the third series the percentage of carbon dioxide in the expired air was at first very low, both at rest and during exercise. In the case of the bronchitic subjects C. and G. it rose a little during the following days with rest in the ward and without any special treatment, but rose still more in all the subjects when they went into the oxygen chamber. This further rise was not merely due to the natural improvement of the patients, because it disappeared again soon after they came out of the chamber, rose again during the second period in the chamber, and afterwards again disappeared.

The observations on C. are shown in detail in Table III. Three of the earliest have been omitted because the carbon dioxide determinations were carried out at the end of the second minute of exercise and not at the end of the first and third minutes. On the first occasion of all, on February 21, he over-ventilated and the carbon dioxide output was very high, while the maximum carbon dioxide percentage was 2.0. On February 25 the maximum value was 3.4, on February 26 was 2.9, and on February 28 it was 3.7, as shown in the table.

The carbon dioxide rose to 4.2 per cent. at the end of the third minute of exercise during treatment in the oxygen chamber on March 6 and 8, and the same value was obtained on March 11, forty hours after he had left the chamber and was living in the ward. However, on March 15 and 19, the former a foggy day, these high values were no longer obtained. On March 27, while under treatment with oxygen, high values were again obtained, and on April 1, sixty-four hours after leaving the chamber, the value after the third minute of exercise was higher than those obtained when the patient was not under the influence of oxygen. The mean values during oxygen treatment, during the subsequent period of forty to sixty-four hours and while the patient was in the ward, are also shown. Not only during exercise, but also during rest, the values during and shortly after oxygen treatment were higher than those obtained when the patient was breathing the ordinary atmosphere.

In M., the patient with myocardial disease, the values were much lower than in C., but a similar rise was noticed as the result of oxygen treatment,

though its amount was less. Here again the figures obtained forty to sixty-four hours after leaving the chamber resembled more closely those obtained during treatment than when the patient was living in the ward. Consequently, in order to assess the effect of oxygen, these values have been combined with those obtained during the chamber period and the mean taken. This is expressed by the phrase 'oxygen treatment (all observations)' in the various tables; but the mean of the results obtained from forty to sixty-four hours after oxygen treatment is also given for comparison.

TABLE III.
*Carbon Dioxide Percentage in Expired Air with and without
Oxygen Treatment.*

	Subject.	Rest.	Exercise.		Rest.			
			1st Min.	3rd Min.	2nd Min.	4th Min.	6th or 7th Min.	9th or after Min.
C.	28.2.24 Ward	2.51	2.8	3.71	2.66	2.74	2.43	2.30
C.	6.3.24 Oxygen chamber	2.78	3.76	4.2	2.95	2.68	2.45	2.53
C.	8.3.24 Oxygen chamber	2.54	2.94	4.2	2.88	2.58	—	2.63
C.	11.3.24 40 hrs. later	2.92	3.67	4.22	3.55	2.89	2.95	2.86
C.	15.3.24 Ward	2.53	2.7	3.51	2.83	2.26	2.64	2.48
C.	19.3.24 Ward	2.19	3.05	3.57	2.97	2.51	2.39	2.23
C.	27.3.24 Oxygen chamber	3.07	3.26	4.25	3.22	2.91	3.1	3.19
C.	28.3.24 Oxygen chamber	2.92	3.14	3.81	3.13	2.76	2.96	3.01
C.	1.4.24 64 hrs. later	2.17	3.33	3.8	3.08	2.70	2.56	2.4
C.	7.4.24	2.61	3.03	3.51	3.2	2.9	2.97	2.54
C.	Mean Oxygen chamber	2.83	3.28	4.12	3.05	2.73	2.83	2.84
C.	Mean 40-64 hrs. later	2.55	3.50	4.01	3.32	2.80	2.76	2.63
C.	Mean Ward	2.38	2.90	3.56	2.93	2.53	2.61	2.37
M.	Mean Ward	2.29	2.53	2.78	2.64	2.40	2.16	2.08
M.	Mean Oxygen treatment (all observations)	2.3	2.71	2.87	2.71	2.49	2.44	2.25
M.	Mean 40-64 hrs. after oxy- gen treatment	2.31	2.56	2.85	2.76	2.4	2.37	2.02
G.	Mean Ward	2.82	3.34	3.67	3.37	3.26	3.06	2.93
G.	Mean Oxygen treatment (all observations)	3.47	3.67	4.14	3.84	3.58	3.48	3.48
G.	Mean 16-42 hrs. after oxy- gen treatment	3.42	3.56	4.04	3.79	3.53	3.36	3.39
	6 days after oxygen treatment	3.11	3.56	3.96	3.3	3.34	3.20	3.55

With G. the value obtained nearly six days after oxygen treatment is very similar to that obtained during treatment, and so it has been included with the other values, which are averaged under the heading 'Oxygen treatment (all observations)'. The rise in percentage during and shortly after treatment is almost as great as in the case of C., and the increase in the percentage at rest is even greater.

During the period of oxygen treatment all these patients were investigated outside the chamber, and so it might be thought that the rise in the carbon dioxide percentage was due to some rapid change occurring as soon as the patient left the chamber and began to breathe the ordinary atmosphere. How-

ever, M. McC. Baird has investigated this point, by observing the percentage in the expired air of a bronchitic patient during the same exercise, i.e. six steps a minute for three minutes, carried out in the chamber as well as outside it, and has observed in the former case an even greater rise than we found.

Briggs (6) found a larger rise in the expired carbon dioxide percentage in untrained subjects during muscular work while breathing oxygen than while breathing air, and it was of interest to find out whether the same effect could be observed in students when they were performing the same exercise as our patients. We made observations on three normal students, with the help of Mr. Baird.

TABLE IV.

Percentage of Carbon Dioxide in the Expired Air of Three Normal Students at Rest, and Rise in Percentage with Exercise.

Subject.	Rest.	A. Exercise.				B. Exercise.			
		6 steps a min. for 3 min.		Rest.		18 steps a min. for 3 min.		Rest.	
		1 Min.	3 Min.	2 Min.	5 Min. and After.	1 Min.	3 Min.	2 Min.	5 Min. and After.
	Per Cent.	Ward.							
		Rise of Percentage.							
Fr.	3.31	0.47	0.69	0.09	0.02	0.94	1.02	0.49	0
Ar.	3.06	0.5	0.42	0.28	0.01	1.07	1.38	0.54	0.08
Hu.	3.24	0.41	0.17	0.07	0.02	0.89	1.03	0.05	0.01
Average	3.20	0.46	0.43	0.15	0.01	0.97	1.15	0.36	0.03
		In Oxygen Chamber after Two Hours' Oxygen.							
Fr.	3.17	0.79	0.93	0.45	0.24	1.09	1.47	0.48	0.10
Ar.	2.87	0.46	0.42	(0.23)	0.02	1.07	1.63	0.44	0.08
Hu.	3.05	0.38	0.35	0.08	0.02	0.38	1.6	0.25	0.02
Average	3.03	0.54	0.57	0.25	0.09	1.18	1.57	0.39	0.05

The figure in brackets was interpolated.

Exercises at six steps a minute for three minutes and eighteen steps a minute for three minutes were carried out in the ward, after a preliminary rest period. The observations were repeated after the students had been sitting reading for two hours in the oxygen chamber. In Table IV the rest value for the percentage of carbon dioxide in the expired air is given, and also the rise in the carbon dioxide percentage at the end of the first and third minutes of exercise and during the subsequent period of rest. In every case the rest values were lower in the oxygen chamber than in the ward. The rise in carbon dioxide percentage with exercise was greater in the oxygen chamber in all these subjects at eighteen steps a minute and in the case of Fr. and perhaps Hu. at six steps a minute. The rise was greater at eighteen steps than at six steps a minute. In fact at eighteen steps a minute the absolute values for the carbon dioxide percentage during exercise were, in spite of the lower resting values, considerably higher in the oxygen chamber than outside it; but this could hardly be said to be the case at the lower rate of exercise. The low values

for the rest carbon dioxide percentage in oxygen may be due to the fact that the subjects had been sitting for two hours, while the period of rest was not so long before they entered the chamber. In each observation several values for the rest carbon dioxide were always obtained and the exercise was only carried out when this had become relatively constant. Whatever the explanation of the lower rest values in the oxygen chamber may be, it is abundantly clear that in normal subjects the carbon dioxide percentage in the expired air rises during exercise in oxygen, as the work becomes more severe.

Only three observations were made in the second series on Patients H. and B. at eighteen steps a minute for three minutes, one before oxygen treatment and two during the influence of oxygen treatment. With B., who had greatly improved and could not previously have done this more strenuous exercise, the percentage of carbon dioxide in the expired air was higher at rest with oxygen and a good deal higher during and after exercise, while in the case of H., who had not chronic bronchitis, oxygen did not raise the percentage at all.

We made a single rather curious observation with the patient C., when he was extremely short of breath and suffering from cough. During three successive five-minute periods the average ventilation per minute was 8.6, 8.2, 8.7 litres, and values of 2.36 and 2.21 were obtained for the percentage of carbon dioxide in the expired air. But just before the end of the fifteen minutes and before a sudden fit of coughing, which made it necessary for him to remove the mask, the carbon dioxide was 2.82, while after he recovered it fell to 2.55 per cent., near its previous level. The drum record for the last two minutes of the whole period (Plate 1, Fig. 1, A) shows that the number of respirations in the minute just before coughing had become 25 instead of 22 and the breathing rather shallower, though it was quite as regular as was usually the case with this patient, and the ventilation for the two minutes was almost identical. Hence there was a short period of unusual concentration of carbon dioxide in the expired air, without any accompanying alteration of respiration, and this occurred just before coughing.

The Type of Respiration during Oxygen Treatment.

Third series. On the whole there is very little change in the pulmonary ventilation as the result of exercise during the oxygen chamber period (see Table V). With C. the ventilation during oxygen treatment was a little less at the beginning of exercise, but greater during the subsequent rest period. The diminished ventilation during exercise was accompanied by a remarkable change in the breathing, as is shown in Plate 1, Fig. 1, where tracings are given during the three minutes of work, and for four or five minutes afterwards. Tracing B was taken before oxygen treatment. Tracing C was obtained on the third day of the first oxygen period. Tracing D was obtained on the second day after this period, and tracing E four days later still. Both the tracings taken during the period of oxygen treatment show a remarkable periodicity corresponding to

TABLE V.

Pulmonary Ventilation and Rate and Depth of Breathing with and without Oxygen Treatment (Third Series).

Pulmonary Ventilation.											
Subject.		No. of Observa- tions.	Rest.	Exercise (3 min.).			After Exercise (5 min.).				
				(1)	(2)	(3)	(1)	(2)	(3)	(4)	(5)
C.	Ward	8	7.5	8.7	12.2	12.9	13.8	11.3	11.3	9.3	9.4
C.	Oxygen treat- ment (all ob- servations)	6	9.0	7.5	10.4	12.0	15.5	14.3	12.4	11.4	11.1
M.	Ward	8	9.5	15.4	19.7	21.7	19.8	16.9	14.0	12.6	11.5
M.	Oxygen treat- ment (all ob- servations)	5	10.6	16.2	19.7	23.5	20.5	17.1	15.1	13.8	13.0
G.	Ward	4	7.1	8.2	9.0	10.0	9.3	7.8	7.5	7.2	7.2
G.	Oxygen treat- ment (all ob- servations)	6	7.0	8.4	9.2	10.6	10.1	8.2	7.5	7.4	7.2
Av.	Ward	20	8.0	10.8	13.6	14.9	14.3	12.0	10.9	9.7	9.4
Av.	Oxygen treat- ment (all ob- servations)	17	8.9	10.7	13.1	15.4	15.4	13.2	11.7	10.9	10.4
Rate of Breathing.											
C.	Ward	—	25	28	31	31	28	28	28	27	27
C.	Oxygen treat- ment (all ob- servations)	—	24	25	28	27	29	29	28	28	27
C.	40-64 hours after oxygen treatment)	—	24	21	28	24	32	31	29	29	26
M.	Ward	—	18.5	22	23	23	21	21	20.5	20	20.5
M.	Oxygen treat- ment (all ob- servations)	—	17.5	23	23	23.5	21.5	21	20.5	20	20.5
G.	Ward	—	18	21	20	21	20	19	18.5	18.5	17.5
G.	Oxygen treat- ment (all ob- servations)	—	17	18	19	20	17	17	17	17	16
G.	16-42 hours after oxygen treatment	—	16	18	18	18	16	17	17	16	16
	5½ days after oxygen treat- ment	—	16	17	18	17	19	20	17	16	15
Depth of Breathing.											
C.	Ward	—	300	310	395	415	495	405	405	345	345
C.	Oxygen treat- ment (all ob- servations)	—	375	300	385	445	535	490	440	405	410
C.	40-64 hours after oxygen treatment	—	482	427	391	503	502	507	473	431	473
	April 7, 1924	—	396	316	424	471	586	499	520	394	394
M.	Ward	—	510	700	850	940	940	805	680	630	560
M.	Oxygen treat- ment (all ob- servations)	—	605	705	850	1000	950	815	735	690	630
G.	Ward	—	390	390	450	475	465	410	405	390	410
G.	Oxygen treat- ment (all ob- servations)	—	410	465	510	530	595	480	440	435	450
G.	16-42 hours after oxygen treatment	—	423	467	506	552	590	477	455	448	460
	5½ days after oxygen treat- ment	—	430	511	519	600	503	455	440	415	500

each step, the tracing sinking and the breathing becoming shallow during the act of stepping. In between the steps the breathing becomes deep. This phenomenon is hardly seen in tracings B and E, when the patient was not under the influence of oxygen. The second treatment with oxygen produced a similar, but less obvious change. This alteration in breathing caused the ventilation to be lower than usual during the work period, when the patient was under the influence of oxygen. In the case of G. the values for the ventilation at rest and during exercise are the same, but, as with C., the value shortly after exercise was a little greater during oxygen treatment. Oxygen treatment did not alter G.'s type of breathing, as was the case with C.

In the case of M. the values at rest, during exercise and subsequently, are slightly greater during oxygen treatment than in the ward, but it is doubtful whether the differences are significant. Both C. and G. had bronchitis and M. was a case of myocardial disease. The most striking fact about these figures is that the differences in ventilation were so slight, particularly when the considerable increase in the percentage of carbon dioxide in the expired air is recalled.

However, there were definite differences noticed in the rate of breathing during oxygen treatment in the two bronchitic patients C. and G., especially the former; while practically no difference was noted in M. With C. the rate was less during exercise, and these smaller values were also obtained from forty to sixty-four hours after the oxygen treatment. There was a tendency for the breathing to become a little more rapid again after exercise in the period after oxygen treatment. With G. the breathing was less frequent in oxygen, both during and after exercise. The same thing was noticed sixteen to forty-two hours after oxygen treatment, and even on the sixth day.

As in general the pulmonary ventilation was rather higher during oxygen treatment, and the rate of breathing rather slower, these two have a combined effect in increasing the depth of respiration. In the case of M. the difference was very slight, though the depth at rest was definitely higher with oxygen. With C. the depth of breathing with oxygen was greater at rest, at the end of exercise and during the subsequent rest period. A similar change was observed forty to sixty-four hours after treatment, and on one occasion on April 7, 1924, when there was a complete change in the weather (i.e. the day was hot and the laboratory had a temperature of 18.5°C). With G. the depth of breathing at rest was a little higher with oxygen than without it, and the same thing was observed during and after exercise. The values sixteen to forty-two hours after treatment are also given separately, and the value obtained on the sixth day after the second period of oxygen treatment. These last show the same phenomenon.

Attention was first drawn to this question by noticing the maximum depth of breathing at any time during and after exercise. Curiously enough, this shows a more striking difference than the average figures, and the individual results show how uniform was the effect of oxygen treatment in increasing the

depth of respiration. The maximum depth on each occasion is shown in Table VI, and with C. the average was increased from 490 to 558 c.c. and with G. from 519 to 630 c.c.; but it should be stated that the very high value obtained in the case of C. on April 7, i.e. 586 c.c., has not been included in these figures.

TABLE VI.

Maximum Depth of Breathing with and without Oxygen Treatment.

C.		G.	
Oxygen Treatment (all Observations).	Ward.	Oxygen Treatment (all Observations).	Ward.
602	545	637	492
583	465	590	532
542	453	602	560
492	503	760	492
573	450	590	518
—	550	600	—
—	466	—	—
Av. 558	Av. 490	Av. 630	Av. 519

First series. (Twelve steps for one minute, Table VII.) In the case of B., the two observations before treatment were dissimilar. He complained of feeling more short of breath on the second occasion than on the first, and the respirations were certainly much more rapid and the ventilation much greater. The results during oxygen treatment and subsequently showed a great improvement on this second occasion. They were very similar to those of the first occasion. A similar though slight improvement was noted with S. In the case of P. the pulmonary ventilation was rather less with oxygen, but the frequency remained the same. The same thing was noticed as regards W., but a very great diminution of ventilation and frequency had taken place when he was investigated, from five to eleven days after oxygen treatment. This patient was much more cyanosed than the others examined in the series and was very much relieved while in the oxygen chamber. He improved very rapidly afterwards, probably more rapidly than would have been the case under ordinary medical treatment; this was reflected in the observations carried out. At the beginning of his treatment in the oxygen chamber his respiration was remarkably periodic after exercise.

These patients usually did not show the increase in the depth of respiration that was obtained in the third series, since the ventilation diminished as well as the rate of breathing, so that the depth was often less with oxygen. However, S. did show a slight increase in depth. These patients were certainly less breathless than those of the third series, for they were able to do an exercise of twelve steps in a minute, which the others could not possibly have managed.

Second series. The exercise chosen was eighteen steps a minute for three minutes (see Table VII). Oxygen treatment did not cause any significant alteration in the type of breathing of H. (effort syndrome) or B. (chronic bronchitis). This is perhaps only to be expected in patients who were well enough for this more severe exercise.

TABLE VII
Respiration with and without Oxygen Treatment (First and Second Series).

Subject.	Condition.	No. of Observa- tions.	Pulmonary Ventilation.				Rate.			Depth.		
			Rest.	Exer- cise.		Rest. 12 steps a minute for one minute.	Exer- cise.	Rest.	Exer- cise.	Rest.		Rest.
				2nd.	5th.					2nd.	5th.	
B.	Before oxygen treatment	2	{ 8-0	15-6	18-4	13-1	26	21	600	440	310	
B.	During oxygen treatment and 48 hours later	3	{ 11-5	23-2	18-0	14-0	37	46	620	390	350	
B.	Before oxygen treatment	2	8-9	15-8	15-5	11-3	29	30	553	427	337	
S.	During oxygen treatment	2	9-8	15-6	18-6	11-8	30	28	600	440	310	
S.	Before oxygen treatment	2	13-0	24-1	17-6	13-5	40	36	600	435	380	
S.	During oxygen treatment	2	12-1	22-7	17-2	13-9	35	32	655	435	395	
P.	Before oxygen treatment	2	6-0	13-6	12-2	7-4	25	19	585	520	355	
P.	During oxygen treatment	2	5-3	10-3	9-0	7-7	25	21	400	380	360	
W.	Before oxygen treatment	1	11-9	20-6	17-6	13-7	35	22	590	800	560	
W.	During oxygen treatment	3	9-7	18-1	12-7	10-9	38	23	487	517	420	
W.	After oxygen treatment	2	7-9	14-6	11-2	9-4	27	13	595	600	525	
18 steps a minute for 3 minutes.												
H.	Before oxygen treatment	2	8-8	41-3	24-8	11-7	34	18	1200	950	620	
H.	During oxygen treatment	2	8-8	44-8	29-1	13-4	37	18	1200	940	540	
B.	Before oxygen treatment	1	10-6	35-1	34-0	16-8	32	26	1090	870	580	
B.	During oxygen treatment	2	10-6	36-6	27-3	15-1	31	24	1180	820	605	

Respiratory Exchange at Rest.

The patients were examined sitting in a chair. As the determinations were in no sense 'basal', considerable variation from day to day was only to be expected. Plenty of time was allowed for the respiratory exchange to become constant, and usually it was followed from five minutes to five minutes until this was the case.

All our results on the resting metabolism with and without oxygen during the third series are shown in Table VIII. As would be expected, the effect of oxygen did not cause any appreciable alteration in the volume of oxygen absorbed by the patients of the third series; but in the case of the two bronchitic subjects C. and G. the carbon dioxide output under the influence of the treatment did appear to be increased, particularly at the time of the first treatment. Values for the respiratory quotient above unity were obtained on several occasions. This is certainly a surprising result. At first sight it might be attributed to the sudden change that took place when the patients left the chamber and breathed the ordinary atmosphere. If lactic acid accumulated, carbon dioxide in excess would be expelled. At the same time, we could hardly suppose that such an effect would be noticeable two days later, as was the case with both C. and G.

In the first series treatment in the chamber did not influence the oxygen consumption at rest. Not enough results were obtained in the second series for conclusions to be drawn.

Respiratory Exchange and Respiratory Quotient during and after Exercise.

Third series. The results for the respiratory exchange of the patients are collected together in Table IX. The special difficulties as regards the oxygen consumption in the case of M. are dealt with in the next section.

In the case of C. the carbon dioxide output during work and for ten minutes afterwards—the time taken for the metabolism to reach the resting level—was on the whole greater when he was under the influence of oxygen than at other times; but the figures are rather lower round about the second oxygen period. The same tendency also seems to hold in the case of G., though, owing to his often feeling unable to carry out the exercise, there are only two results when he was not under the influence of oxygen, viz. at the very beginning and at the very end of the period. M. (myocardial disease) cannot be said to show this tendency. Rather higher figures were obtained with oxygen and low values were obtained on two occasions after the first oxygen period, when the exercise was six steps a minute, viz. 3,282 and 3,565, but other higher ones, viz. 4,703 and 4,862, were also obtained without oxygen, so that the high figures were not due to the oxygen.

The percentage of the total carbon dioxide which was eliminated during the three minutes of work has also been calculated. In the case of M. and

TABLE IX (continued).

Percentage of the total Carbon Dioxide which was eliminated during the 3 Minutes of Work.															
C.	30	24	28	25	—	23	34	—	31	30	27	—	—	—	—
G.	—	—	44	44	—	41	41	—	—	43	44	—	—	—	—
M.	—	—	35	33	—	28	30	27.5	29	28	32	29	33	84	—
	—	31	31	—	—	—	—	—	—	—	—	—	—	—	—
Total Oxygen absorbed during 3 Minutes' Work and subsequently.															
C.	4920	5010	4524	4790	4496	3860	4066	—	5130	4000	4750	4360	—	—	—
G.	—	—	3284	3460	2794	3070	2840	—	—	2460	2790	2205	—	—	—
Percentage of the total Oxygen which was absorbed in the 3 Minutes of Work.															
C.	39	33	37	33	35	42	39	—	36	40	42	39	—	—	—
G.	—	—	58	53	59	51	58	—	—	54	54	56	—	—	—
Extra Carbon Dioxide due to Exercise.															
C.	1092	791	1704	2425	—	1004	475	—	—	866	1933	1523	—	—	—
G.	—	—	641	943	—	628	566	—	—	462	717	443	—	—	—
M.	—	—	2408	2001	—	—	1129	887	1469	1488	1824	1020	1084	2453	—
	—	1353	1601	—	—	1380	718	—	—	—	—	—	—	—	—
Extra Oxygen.															
C.	1596	1832	1902	2340	1282	1273	1578	2515	—	1112	2060	1811	—	—	—
G.	—	—	1452	1574	972	1373	1002	—	—	741	867	737	—	—	—
Respiratory Quotient due to Exercise.															
C.	0.68	0.43	0.9	1.08	—	0.79	0.3	0.56	—	0.78	0.94	0.84	—	—	—
G.	—	—	0.44	0.6	—	0.46	0.57	—	—	0.62	0.83	0.60	—	—	—
Apparent Absorption of Oxygen in the case of M. (Myocardial Disease) during 3 Minutes' Work and 2 Minutes afterwards.															
M.	—	—	1180	2170	2776	3036	1676	74	212	2830	836	1286	902	1470	—
	—	1680	1396	—	—	2230	357	—	—	—	—	—	—	—	—

G. the percentage fell within a narrow range and was not affected by oxygen. With C. rather low values were obtained for the first oxygen period, viz. 25 and 23 per cent., and were associated with the remarkable alteration in the type of breathing already described.

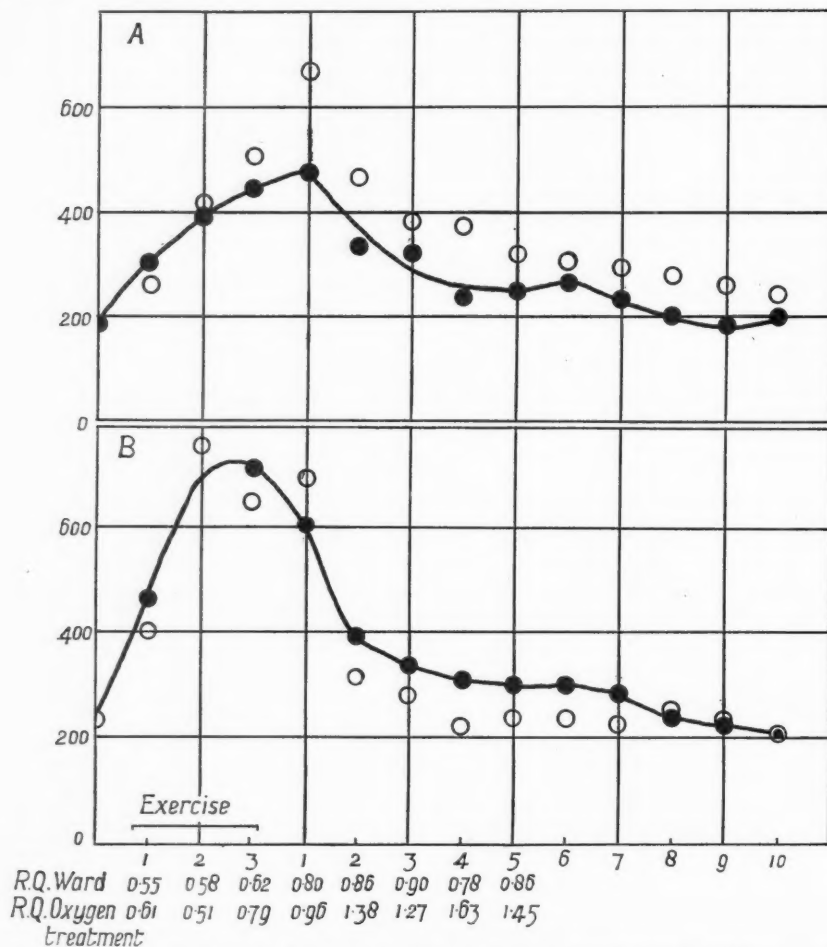


FIG. 2. Patient C. A. Carbon dioxide eliminated at rest, during three minutes' exercise, and subsequently. B. Oxygen intake. Ordinates, carbon dioxide or oxygen in c.c. Abscissae, time in minutes. ● Patient in ward. ○ Patient under influence of oxygen. The respiratory quotients for different minutes are printed beneath the figure. In this and subsequent figures, but not in the tables, the volumes of oxygen and carbon dioxide are measured moist at room temperature and atmospheric pressure.

Oxygen treatment caused no certain effect on the total oxygen intake, either in the case of C. or G., nor had it any influence on the percentage of the total oxygen absorbed in the three minutes of work. In Table IX the results for the extra carbon dioxide and extra oxygen due to the work have also been tabulated. The results are extremely irregular, perhaps because the exercise

was so slight that the total metabolism was not much greater than the rest metabolism would have been for the whole period of the exercise, and experimental errors would be magnified by the subtraction necessary to give the extra metabolism. However, on calculating the respiratory quotient from these figures it certainly is rather striking that in most observations on C. the value is higher under the influence of oxygen than at other times. In a previous

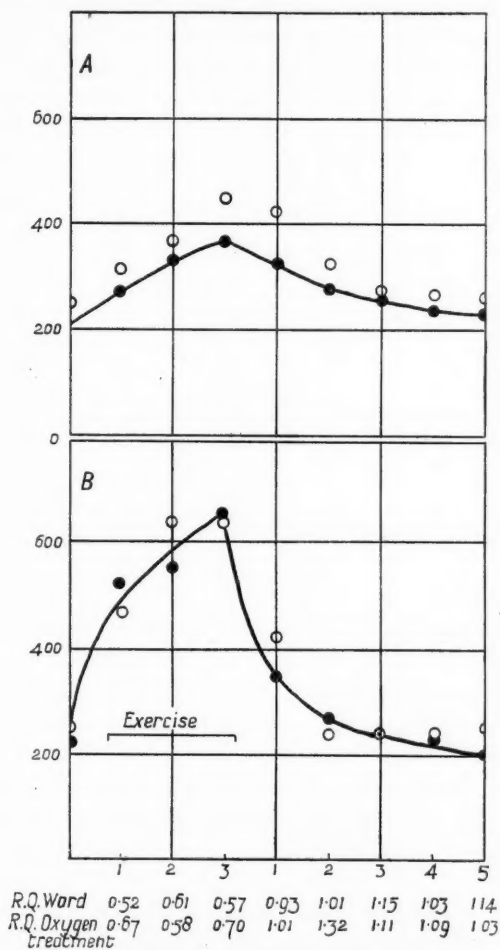


FIG. 3. Patient G. For description, see Fig. 2.

paper we have suggested that owing to his breathlessness and cyanosis there was ordinarily some modification in the metabolism due to exercise in this patient, and his higher quotient during oxygen treatment certainly fits in with such a view. The higher quotient with oxygen is not as certain in the case of G. at the lower rate of work, but we have only two observations with this subject, when he was not under the influence of oxygen, for comparison.

In order to gain an insight into the rate of excretion of carbon dioxide and absorption of oxygen in these subjects during exercise and subsequently, both when they were and when they were not under the influence of oxygen, we have plotted out the average results of all observations in the two conditions. In the case of C. (Fig. 2) the carbon dioxide curve under oxygen is well above the curve without oxygen from the third minute of work onwards. Relatively low carbon dioxide excretions were recorded for the first and second minutes of work, corresponding to the low pulmonary ventilation already described. The carbon dioxide curve under oxygen treatment certainly does not fall any more rapidly to the base-line than the other one. The curve for the absorption of oxygen under treatment, however, behaves differently. It rises at the same rate as the other curve, but falls quicker, reaching the base-line by the fourth

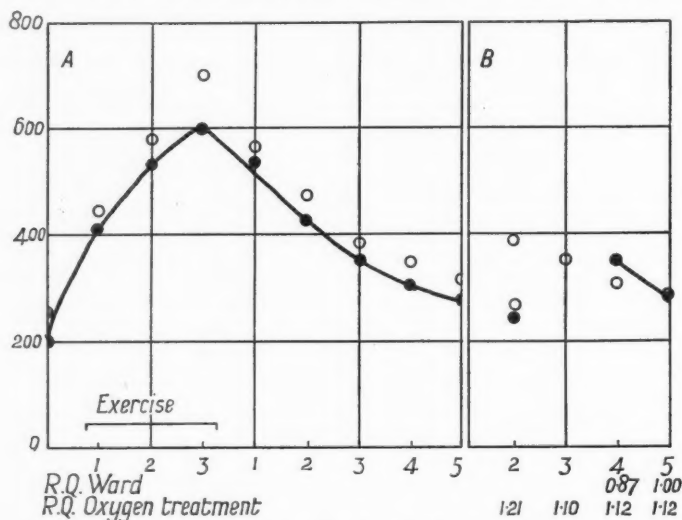


FIG. 4. Patient M. For description, see Fig. 2. The lower circle and dot placed at the second minute in B are the rest values before the exercise.

minute of rest. The respiratory quotient (shown beneath Fig. 3), with and without oxygen, was about the same at the beginning of exercise and was quite low, but at the end of exercise it was much lower when the patient was without oxygen.

In the case of G. (Fig. 3) the carbon dioxide curve with oxygen is also rather above the other curve, and, as is the case with C., the oxygen curve, under oxygen treatment, falls more rapidly to the rest value, so that the respiratory quotient at the end of exercise is again rather higher.

The carbon dioxide results for M. are shown in Fig. 4 at A. Both curves fall at about the same rate, but they have not reached the resting value at the end of five minutes after exercise. A few oxygen values in the second, third, fourth, and fifth minutes of rest are also shown at B, when the apparatus had again begun to measure the oxygen intake accurately. The curve under oxygen

treatment would appear to be slightly lower than the other one and the respiratory quotients higher.

First series. Eight observations were made on Patient B. The following were the results for the extra oxygen due to the work (twelve steps in one minute). Before oxygen treatment on successive days, 2,575, 1,760 c.c.; on the third and fifth days of treatment, 1,180, 1,510 c.c.; within forty-eight hours of coming out, 1,278; from five to twenty-two days after coming out, 1,480, 1,528,

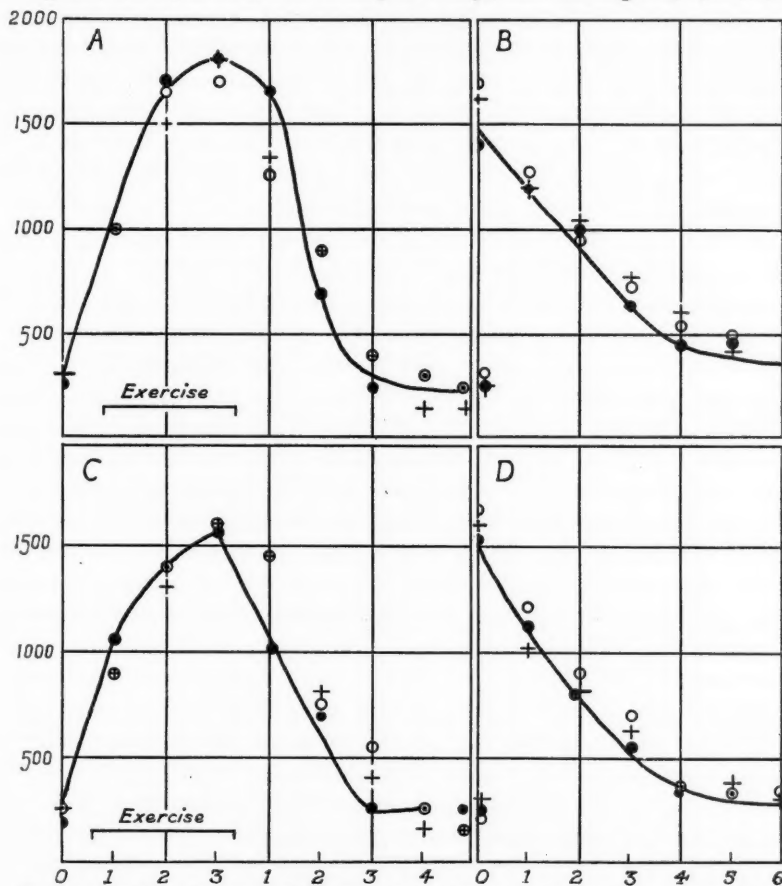


FIG. 5. A and B. Oxygen and carbon dioxide figures for Patient B. C and D. Ditto for Patient H. For further explanation, see Figs. 2 and 4. + represents a second observation under oxygen treatment. \circ and \oplus represent two identical values obtained in different series. and 1,124. This certainly suggests a fall in extra oxygen consumption with treatment, persisting to a great extent afterwards. In the first two observations, i.e. before oxygen treatment, the average gross oxygen consumption for the second five minutes of rest after the exercise was still above the resting value, while in all the other observations, during treatment and subsequently, the oxygen consumption had reached the resting value by the end of the first five minutes of rest.

The extra oxygen consumption for S. on successive days before treatment was 1,365, 1,440 c.c.; on the third day of oxygen treatment 1,094, while on the fifth day of treatment he had a severe acute coryza and was feeling far from well, and the value was much higher, viz. 1,744 c.c. This coryza did not cause the ventilation to increase. The gross oxygen consumption of this patient in all observations fell to the resting value quite quickly, i.e. by the third minute after exercise. The high value obtained for S. during his coryza and the low values obtained with B. after oxygen suggest that the oxygen acts by improving the physical condition of the individual. Our results with P. also suggest a diminution in the oxygen absorption during oxygen treatment. In the case of W. there was no evidence of alteration in the oxygen consumption; but we have only one not very reliable result before oxygen treatment was begun. With this patient exercise caused much less extra oxygen to be absorbed than normal, so that his efficiency was apparently high.

Second series. The two patients B. (bronchitis) and H. (effort syndrome) were comparatively fit, since they could manage an exercise consisting of eighteen steps a minute for three minutes. In each case we have one observation before treatment, one on either the second or third day of treatment, and one on the day following the chamber period. In the case of B. the extra oxygen on these dates was 4,930, 4,775, 4,080. Unfortunately in these two patients we only have values for the carbon dioxide of the third minute of work and the subsequent rest period, and we have calculated the extra carbon dioxide for this period. In the case of B. these figures were 3,316, 3,420, 3,702 c.c. In the case of H. the extra oxygen was 4,600, 4,560, and 4,390, and the extra carbon dioxide 2,790, 3,328, and 2,862. In both cases treatment tended towards a diminution of the extra oxygen consumption and slightly increased the extra carbon dioxide output, so that there is little doubt that the respiratory quotient for the work would have been increased if we had had sufficient data to make the calculation worth while.

The individual results for the oxygen and carbon dioxide are shown in Fig. 5. The two sets of observations made when the patients were under the influence of oxygen were extremely similar to one another, but it cannot be said that at this rate of exercise oxygen treatment caused either the curve for oxygen absorption or carbon dioxide output to fall more quickly to the resting value.

Special Difficulties with Patient M. (Myocardial Disease).

M.'s oxygen consumption during exercise, as measured through the meter, was very much lower than the others, and this reading cannot be taken as the real value. The result was due to a defect in the closed circuit method, the accuracy of which depends on the volume of the contained air being kept constant. This is checked by the fact that the spirometer and the writing-point on the drum move up and down about the same mean position. As long as this position is unchanged, the meter is registering accurately the

oxygen consumption. With most subjects there was no difficulty in getting this level constant, once we had learnt the right pressure for the oxygen delivery, nor was there any difficulty with M. at rest; but soon after he began to take exercise the level on the drum fell (see Plate 2, Fig. 6, B). This means that the spirometer rose, because air was being driven from his lungs into the closed circuit. There can only be two possible causes of this: (1) the mean position of his chest came nearer to the expiratory position, either by falling in of the ribs or rising of the diaphragm, a view for which we were unable to find any evidence; (2) air was driven out of his chest by some process, such as engorgement of the lungs with blood owing to failure of the left side of the heart, or to dilatation of the heart.

As far as the instrumental side of the difficulty is concerned the explanation is easy. The extra air from the chest, which raises the spirometer, increases the pressure inside the circuit and prevents the intake of fresh oxygen, and the subject therefore obtains oxygen from the air in the circuit, reducing its percentage. The return of air from the apparatus into the chest will make the spirometer come back to its original level; and when this has occurred oxygen will be drawn into the circuit with each breath as before. But, because during the rise of the spirometer the place of the oxygen used up from the circuit has been taken by the extra air added from the chest, the lag in the oxygen intake will not be remedied; even when the oxygen consumption per minute is again recorded accurately, the error in the total oxygen consumption will remain. The phenomenon has not been met with in any of the other subjects referred to in this paper, and is mentioned here because of the striking effect which oxygen had in relieving it. This is well shown by comparing the two tracings shown in Plate 2, Fig. 6. Tracing A was obtained on the third day of oxygen treatment, and there was hardly any fall in the tracing. Tracing B was taken eleven days after the first oxygen period. The magnitude of the change may be roughly gauged from the figures for the apparent oxygen consumption during three minutes' work and two minutes afterwards (Table IX, at bottom). The lower the figure, the greater the amount of air driven out of the chest. The change was obviously much less under the influence of oxygen. Even at four steps a minute the same difficulty with the oxygen was found. Only on two occasions were figures obtained for the oxygen consumption which seemed at all reasonable. On both these occasions M. was under the influence of oxygen.

To find out whether the change was due to the position of the chest being altered, a stethographic tracing was taken during one observation (Plate 2, Fig. 6, B). The respiratory tracing remained level during the first minute and a third of exercise. It then began to fall and reached its lowest point during the latter half of the third minute. As soon as rest began it climbed back during two and a half minutes to the original level. If the phenomenon were due to pulling in of the chest, we should have expected a fall in the stethographic record during the exercise to coincide with the respiratory tracing; but obviously this

did not take place. A fall only occurred at the end of exercise for purely mechanical reasons, i.e. when the patient sat down.

We have not yet been able to prove that the phenomenon was due to temporary circulatory stasis; but this we hope to investigate. The matter is of importance, as it may mean that the apparatus will provide a new method for investigating the beginning of acute circulatory failure. Some of our observations are, however, very suggestive in this connexion. On one occasion the fall in the tracing began at the beginning of the second minute of exercise, i.e. about the seventh step, and at this point the patient noticed praecordial pain. Nearly two years after these observations M. was still in much the same state of health, though he thought he had benefited greatly from the oxygen treatment. When tested at six steps a minute he again showed this drop in the drum record, and on each occasion the drop started about thirty seconds before he signalled the onset of his praecordial pain. If there was any change in the vital capacity at this time it would support our hypothesis, because the lowered vital capacity of cardiac disease is probably due to congestion of the pulmonary capillaries causing a diminution in the residual air of the lungs. Two observations were made; on the first occasion he finished the third minute's exercise and rested for a fourth minute before he was tested, and on the second he was tested at once. In 1924 his vital capacity was 4 litres; two years later, on the day he was tested it was generally 3.0 and once 3.3 litres, and his pulmonary ventilation at rest, which was previously 9.5-10.6, had risen to 11.2 litres, but he had walked to hospital an hour before the last determination. On the first occasion, when he was tested after the onset of praecordial pain, the vital capacity had fallen to 2.0, and as soon as the pain was better it was 3.1 litres. On the second occasion, when tested immediately after the onset of pain, it was 2.7; about a minute later, when he still had the pain, 2.6; and after about another minute, when he said the pain had gone, 3.3 litres. These figures are certainly suggestive, though not conclusive, because the breathlessness or the pain itself might lower the vital capacity.

To summarize, we have found in this patient that exercise often caused an expulsion of air from the chest with a corresponding diminution of the volume of air in the lungs. This phenomenon was sometimes associated with praecordial pain. It was not due to any alteration in the position of the ribs and it was much less striking when the patient was under the influence of oxygen. We attribute it provisionally to acute circulatory stasis.

Influence of Oxygen on the Pulse-rate.

Only in the three subjects of the third series are there sufficient results to make this worth considering. The pulse-rate, especially during exercise, was very variable from day to day. The subject has already been briefly considered in our first communication. Oxygen treatment did not appear to have any influence on the pulse-rate during exercise.

Discussion.

In a previous paper (2) we have described a twofold response of the respiration to exercise in patients with bronchitis. In all cases the respiration is shallow and tends to be rapid during rest. The rapidity is greatly increased with exercise, but in one group of patients the depth also increases, and so the pulmonary ventilation becomes very much higher than normal. In a second group the breathing remains shallow with exercise, so that the pulmonary ventilation is less than normal. We have tentatively put forward the view that in the first group the bronchitis is associated with emphysema, while in the second group there is an asthmatic element also present which prevents the breathing from becoming deep. In this group breathlessness is experienced with the mildest of exercises.

The effect of oxygen on bronchitis seems to vary according to the group to which the patient belongs. Thus Beddard and Pembrey (3) found that with oxygen the pulmonary ventilation was reduced and the breathing became shallower, and this was also observed by us with the late G. H. Hunt (4). In all these cases the patients were at rest when tested, but in this paper the results during and after exercise are also described. In the observations on the patients of the first series, who were not extremely short of breath, oxygen treatment frequently caused the pulmonary ventilation to be reduced, and the respiration to become less frequent with no very definite alteration in the depth of breathing. In two patients of the third series, who were very breathless, oxygen treatment did not cause any alteration in the ventilation, but diminished the frequency and increased the depth. Comparing these facts with the conclusions referred to above, we may suggest that the effect of oxygen in emphysema is primarily to diminish the frequency of respiration and so to lower the pulmonary ventilation without altering the depth, which is already maximal, while with asthma it acts both by slowing the breathing and increasing the depth. Its action in emphysema may be due to some improvement that takes place in the epithelium, by which the exchange of gases is rendered more efficient, though we cannot exclude circulatory improvement; while its action in asthma may be to cause a relaxation of the spasm and so to enable a deeper and more efficient ventilation to be carried out. The percentage of carbon dioxide in the expired air would then be increased, as we have found to be the case.

Some evidence has been obtained that under ordinary circumstances in a breathless bronchitic patient there is a qualitative alteration in the metabolism due to exercise with a lowering of the respiratory quotient; while after oxygen treatment the respiratory quotient due to exercise is higher. Our third series of observations showed that this was due to an increase in the carbon dioxide output due to oxygen treatment, while a slight increase was probably also present in the less breathless patients of the second series. In these there was also a slight diminution in the oxygen intake, and the same thing was usually

noticeable in the patients of the first series. These results for the oxygen absorption are not quite as clear-cut as our other findings, but Briggs (6) also found that the oxygen intake was less when exercise was carried out in oxygen than it was in air.

In this paper we have commented on the increase in carbon dioxide percentage of the expired air brought about by oxygen treatment. This must be caused by two factors: (1) a lowering in the pulmonary ventilation, as is well illustrated by Case 42 in a previous paper (4, p. 271): (2) an increase in the output of carbon dioxide, much as we have found in Case C. of the third series.

The rate of absorption of oxygen fell more rapidly with oxygen treatment in the more breathless patients; but in patients who could undertake an exercise consisting of eighteen steps a minute for three minutes, oxygen treatment did not alter the rate of fall of oxygen absorption. Oxygen treatment did not appear to make any difference in the rate of fall of the carbon dioxide output after exercise.

The problem as to how long the effect of oxygen persisted after the treatment was over is a double one. In the first place, the changes in respiration already described, and particularly the rise of carbon dioxide percentage in the expired air, were not only observed in the patients of the third series during oxygen treatment, but, as we found to our surprise, they could be appreciated for two or three days afterwards, though they then disappeared. This would suggest that there is a temporary effect due to oxygen coming on rapidly at the beginning of treatment and before the onset of any clinical improvement that may occur in the patient's condition—similar to the change that Briggs found in unfit men when they were taking exercise in oxygen, and that we found with our normal students in the oxygen chamber.

In the second place, we have to consider whether oxygen produced any long-standing benefit in bronchitic patients. Obviously oxygen cannot directly cause the disappearance of pathological structural changes in the lungs; but if the infective process and the resistance of the organism against it are so nicely balanced as to produce a chronic disease, oxygen may increase the resistance and so terminate the infection, or if an acute bronchitis supervenes on a chronic state, oxygen may help towards the cure of the acute attack. The improvement in the type of respiration of W., which began with the oxygen treatment but continued afterwards, coincided with the great clinical improvement that was noticed in his case. A similar suggestion has also been made in the cases of B. and S. In this connexion we must consider the clinical history of all our patients.

But here at the outset we are face to face with two difficulties that are always present when the effect of treatment is estimated clinically: (1) the difficulty of being certain on clinical grounds that the patient really is better and does not merely think he is better, and (2) being certain that any such improvement is *propter hoc* and not merely *post hoc*. Full clinical details have been given. Summarizing these, we may say that all the patients except S. felt

better with the treatment for a period varying from a few days to some weeks. Over a year later B., P., and W. said they had not been so ill as when they were admitted to the hospital previous to oxygen treatment. H. said that his condition was variable; M.'s condition was no worse and he himself thought he had benefited; C. was better a month afterwards, but did not reply a year later, and G. had died. S.'s case was complicated by the fact that he had as septic a mouthful of teeth as is ever met with, and he refused to have them removed. In the case of C. and G. the sputum was measured, and a diminution was noticed especially in the case of C. (Table X), and this agreed with the impression we had gained from some of the other patients.

TABLE X.

Average Daily Volume of Sputum in Ounces before, during, and after Oxygen Treatment.

	Before Treatment.	Oxygen Treatment.	After Treatment.		Second Oxygen Treatment.	After Second Oxygen Treatment.
G.	0.6	0.8	0.5	1.0	0.3	0.8
C.	6.8	6.3	2.3		0.9	3.5
	(10)	(8.5)	(4)		(15)	(4)
	(4)	(4)	(0.5)		(0.5)	(3)
	Before Treatment.	Oxygen Treatment.			After Treatment.	2-4 Weeks Later.
Pal.	1.6	0.56	0.1	1.2	0.05	0.0-0.25
Sto.	1.8	2.7	1.95	1.4	0.6	0.0-0.6
Box.	0.8	0.9	0.35	0.2	0.0	0.0
Web.	0.8	0.5	0.3	0.3	0.2	0.25-0.3

The periods vary from five to eight days.

It was considered worth while to investigate this and other clinical points in a new group of four bronchitic patients during a longer period of oxygen treatment. Consequently two patients (Box. and Web.) were treated in the chamber from Monday to Saturday, i.e. five full days of two successive weeks, and from Monday to Friday of the third week. They remained in the chamber each day from 10 a.m. to 12 noon, 1.45 a.m. to 4 p.m., and 7 p.m. to 5.30 a.m. The third patient (Pal.) noticed headache in the chamber and slept in the ward for six nights during the second and third weeks. A fourth patient (Sto.) stayed in the chamber for the morning and afternoon periods during the third week and slept in the chamber for four nights during the later half of the period.

D. R. Web., aged 27. Had a touch of 'gas' on the Somme in 1916. Cough began, but he continued doing hard work in the army till demobilization in 1919. Shortness of breath with exercise, noticed March 1924; had to give up football; it made him feel dead-beat, and he then began to cough.

Admitted under Dr. Poulton, May 4, 1925. Signs suggestive of fibrosis at left base, but generalized bronchitis was also present. Mucopurulent sputum. Hb. 102 per cent. Red cells 5.06 millions per c.mm. (Dr. Carter Braine).

P. Pal., aged 47. Cough ever since he could remember. Worse in winter. Short of breath for sixteen years, but worse since Christmas 1924, when he had influenza with pleurisy and bronchitis. Coughing and hurrying, bringing on mid-sternal pain, made him feel faint and unable, for the time being, to eat.

Admitted May 4, 1925, under Dr. Poulton: slight cyanosis of lips and tongue; cheeks and ears full red colour. He had obvious difficulty with breathing. Emphysematous chest. Weak breath sounds and rhonchi all over of various pitch, heard especially during expiration. Pain in chest relieved by amyl nitrite (one observation). Hb. 100. Red cells 5.1.

T. Sto., aged 62. Bronchitis all his life. Swelling of feet with attacks noticed a year ago. Had to give up work nineteen days before admission.

Admitted April 20, 1925, under Dr. Poulton. Cyanosis of lips, tongue, cheeks, and nails. Palpation lower. Pulse 90-110. Emphysematous chest. Rhonchi all over, prolonged expiratory sound. Oedema had disappeared by May 11, when oxygen treatment began.

P. Box., aged 43. Gassed 1916, and had coughed ever since.

Admitted May 19, 1925, under Dr. Poulton. Much sputum, no tubercle bacilli found; X-ray showed some infiltration in both lungs, with large root shadows on both sides. Slept badly; got attacks of rage and weeping, tremor of hands, and mask-like face. When previously admitted he spent five nights, April 7 to 12, in the oxygen chamber and said he obtained the first decent sleep he had had for months. May 11, before three weeks' oxygen period, hands cold and blue. Breath sounds faint; high-pitched rhonchi all over during expiration. Hb. 94. Red cells 4.94.

The patients were in the ward for at least a week previous to the beginning of the treatment, and the clinical results may be summarized under the following headings. No alteration was found in the haemoglobin or in the number of red cells in the patients investigated, viz. Box., Pal., and Web.

Patients' feelings. The appetite was improved in all patients during treatment. Dr. G. H. Hunt informed us that this was a common experience during his observations at Cambridge. Pal. felt about the same, the others better after treatment. Box. had not felt so well for two years.

Body-weight. The increase of average weight during treatment over the previous average weight was for Pal. 2.2 lb.; for Box. 8.4 lb.; for Sto. 2.3 lb.; for Web. 5 lb.

Cough. Cough was less in all patients while in the chamber, and it was looser. Box. noticed he began coughing immediately he came out of the chamber for meals.

Physical signs. The local signs at the left base remained about the same in Web., though whispering pectoriloquy was not heard at the end of treatment. In the other subjects the rhonchi had nearly completely disappeared at the end of the treatment. However, in the case of Box. and Pal. they had returned as before by the end of the next week.

Holding of breath after a normal expiration was tested before admission and at different times during treatment and afterwards. In all cases it steadily increased, and the increase was maintained for a week or so afterwards; e.g. with Box. before treatment, 7 secs., 6 secs.; after five days, 8 secs.; after ten days, 9 secs.; at the end of treatment, 19 secs.; one week later, 25 secs. The increase in these values in our patients was too great to be attributed to practice alone.

There can be no doubt from the foregoing that clinical improvement occurred in these patients. In the case of Sto., who spent the shortest time in

the chamber and was actually ill with heart failure on admission, it is not possible to be certain that the oxygen helped matters, since before treatment he was showing rapid improvement in the ward; but he himself certainly believed in it. The other three patients were in a chronic condition of ill health before coming in, and their improvement may with more certainty be attributed to the chamber.

Earlier clinical observations on two patients with chronic bronchitis and emphysema, Lam. and Per., aged 64 and 66, may be mentioned here. They remained in the chamber four days. At the end they felt less short of breath, and Per. said his cough improved. The vital capacities (2.0 litres and 2.35 litres) did not show any significant alteration and there was no alteration in the other quantities measured, such as haemoglobin percentage, blood-pressure, expansion of the lungs, &c. Both patients noticed a headache at the beginning of the treatment.

From all these results we may say that, although a stay of four days in the oxygen chamber produced a measurable alteration in the respiratory data, indicating improved function, it required a longer stay to produce much amelioration of the clinical features.

Consideration of the effect of treating bronchitic patients in an oxygen chamber naturally calls to mind previous observations on the effect of treating similar cases in a compressed air bath, since the effect of increasing atmospheric pressure is to increase the pressure of oxygen. Favourable clinical results in cases of emphysema, bronchitis, and asthma treated in the bath at the Brompton Hospital have been claimed by Dr. Theodore Williams (7). Calculation shows that the oxygen pressure would be equivalent to about 35 per cent. oxygen at atmospheric pressure, or rather under the value employed by us.

Conclusions.

1. Patients with chronic bronchitis and emphysema have benefited by residence for a period of from one to three weeks in a chamber containing about 40 per cent. of oxygen. The improvement was shown by their sensations and by diminished cough, sputum, and breathlessness; by their increase of appetite and body-weight; by the disappearance of rhonchi and by the increased time of holding the breath. In some patients these effects quickly wore off; in others they appeared to last, partially at any rate, for months.

2. The effect of treatment was to cause an increase in the percentage of carbon dioxide in the expired air during rest and exercise, and this effect was observed in certain cases for at least two days after leaving the chamber.

3. Some evidence was obtained that in the less breathless type of patient, whose bronchitis was not associated with bronchial spasm, clinical improvement with oxygen was associated with a diminished intake of oxygen during exercise. The frequency of the respiration certainly became less, so that the ventilation, which without oxygen was excessive, reached normal limits.

4. In patients with severe breathlessness whose bronchitis was associated with bronchial spasm, exercise caused both a lowering of the rate of respiration during exercise and an increase in the depth, so that the pulmonary ventilation was unaltered. There was some evidence that the output of carbon dioxide was increased, so that the respiratory quotient during exercise reached the normal level. The oxygen intake did not appear to be diminished; but the evidence was not very satisfactory because, since only the lightest of exercise could be undertaken by these subjects, the extra oxygen bore only a relatively small proportion to the total oxygen absorbed.

5. Some evidence was obtained in a case of myocardial disease that exercise caused a temporary stasis of blood in the lungs. This was sometimes accompanied by a feeling of praecordial pain and by diminution in the vital capacity. This phenomenon was much diminished during oxygen treatment.

We should like to thank the physicians at Guy's Hospital, who have allowed us to investigate cases under their care, and all others who have helped us in our work, in particular Dr. Bowell and Dr. Carter Braine for kindly examining the blood in some of our patients. We owe a special debt of gratitude to Miss Hawes, the Sister in charge of Addison Ward, without whose cordial co-operation an investigation of this kind would have been impossible, and to Mr. F. H. Muir for his accurate data as to the composition and temperature of the air in the oxygen chamber.

APPENDIX.

A Description of the Oxygen Chamber at Guy's Hospital.

The oxygen chamber in which the treatment was carried out was built by the Works Department of Guy's Hospital to the directions of the late Dr. G. H. Hunt, who had worked with a similar chamber at Cambridge on the effect of oxygen treatment on soldiers who had been gassed (5). Walls and roof were built of plate glass set in a teak framework.

One corner was divided off so as to contain the boxes for absorbing the carbon dioxide, and pipes for maintaining the circulation of air were led from here to a fan in the basement; the return air was pumped through a water-tank for purification. The entrance was at the side of this section and consisted of a double air-lock with three doors. Each air-lock could just hold two or three men, but if it was necessary to take in a stretcher two doors had to be opened at once. The doors were opened and closed by a central circular handle; when this was turned, four radiating metal bolts with wedge-shaped extremities were driven into specially prepared slots on the frame. By such means the door was closed tightly against some rubber tubing attached round the framework. A similar mechanism is commonly employed for closing the door of a steam oven.

The absorbing chamber and the entrance occupied about one-quarter of the total space, leaving an L-shaped chamber which comfortably held three beds.

Twice a day when the chamber was in use oxygen was admitted from cylinders into the ventilation pipe in the basement so as to raise the percentage to its original level. To avoid waste of oxygen in filling, the oxygen was run through the ventilation shaft into a large bag inside the chamber, the surplus air being allowed to escape through holes in the framework, which were

ordinarily closed with U-tubes containing oil to act as safety-valves. When enough oxygen had been admitted, the holes were closed up and the bag emptied into the chamber. The air in the chamber was mixed with a second fan in the chamber. Six cylinders containing each one hundred cubic feet of oxygen were generally used for the first filling, and this raised the oxygen in the chamber to about 50 per cent. or rather less. Generally fresh oxygen was admitted each morning and evening, most often three but sometimes six cylinders being used on each occasion. Analyses of the air were made once or twice daily. The percentage of carbon dioxide was determined by a Haldane's mine-air apparatus and the oxygen by his smaller gas analysis apparatus containing a cylindrical burette.

The carbon dioxide was absorbed by passing the air through trays of soda-lime and flake caustic soda. This appeared to work satisfactorily, as the carbon dioxide percentage in the chamber remained steady at about one-half per cent.

Calculation showed that absorption of oxygen by the patient would not account for the whole fall in the percentage of oxygen in the chamber, which must have been partly due to the opening of the door and to leaks. That the fall due to leaks was often not great is shown by two (of several) observations when the chamber was filled with oxygen and did not contain any patients. On one day the oxygen percentage was 32.4 at midday, 31.8 that evening, and 28.8 the next morning; on another it was 35.8 at midday, 31.9 that evening (the door having been opened ten times), and 30.1 the next morning.

Taking these points in rather more detail, we found that during the first series in March 1923 the oxygen percentage after filling averaged 45 per cent. (9 analyses) and varied from 43 to 50; while its level before filling averaged 38.4 (3 analyses), a fall of about $7\frac{1}{2}$ per cent. in the twelve hours. The average percentage of carbon dioxide was 0.41. The temperature did not vary widely, and wet and dry bulb readings averaged respectively 54° F. and 58° F. outside and 51° F. and 63° F. inside.

During the second series of observations (June 5-9) the average oxygen percentage before and after filling was 48.2 and 36.4, but there were fewer observations and they were made less regularly; the average percentage of carbon dioxide was 0.6.

During the third series of observations the chamber was used twice, from March 3-9 (1924) and from March 24-29. The first time the oxygen percentage averaged 44.5 after filling (12 analyses) and only 27.3 before filling (8 analyses). The carbon dioxide averaged 0.45 per cent. and the dry and wet bulb readings inside the chamber and outside in the ward averaged respectively 58 and 55.5 inside, and 56 and 52 outside, showing that the atmosphere in the chamber approached the outside conditions more closely than in the first series of observations.

During the second period the oxygen percentage started higher, but the fall was greater; one and sometimes two other patients were in the chamber. The average figures were 55.5 (9 analyses) and 37.0 (7 analyses). The average percentage of carbon dioxide was also a little higher, viz. 0.55. The average figures for the dry and wet bulb readings were 57 and 49.5 outside and 59.5 and 57 inside.

In the last series of observations, when the chamber was used during three successive weeks, the average percentage after filling was 48.6 (maximum 51, minimum 44, in nineteen observations), while the average value before filling was 37.1 (maximum 40.5, minimum 35, in five observations).

On the whole the oxygen chamber answered satisfactorily for the treatment of the chronic cases described in this paper, although it was not easy to raise the average percentage of oxygen during the twenty-four hours much above 40 per cent. Headache was complained of by some of the patients, and sometimes by nurses, when they stayed in the chamber some hours to attend acute

cases. At present we have no certain knowledge of its cause. One possibility was that the oil used for lubricating the fan might have undergone slow oxidation in the enriched atmosphere, and certainly on one or two occasions a mist was noticed in the chamber. This could be prevented by passing the incoming air through tins containing charcoal. On one occasion we replaced all the oil by glycerin, but although the fan worked well to begin with, while kept in continuous motion, the vanes stuck on restarting the fan after a day or two's break, and oil had to be resorted to again.

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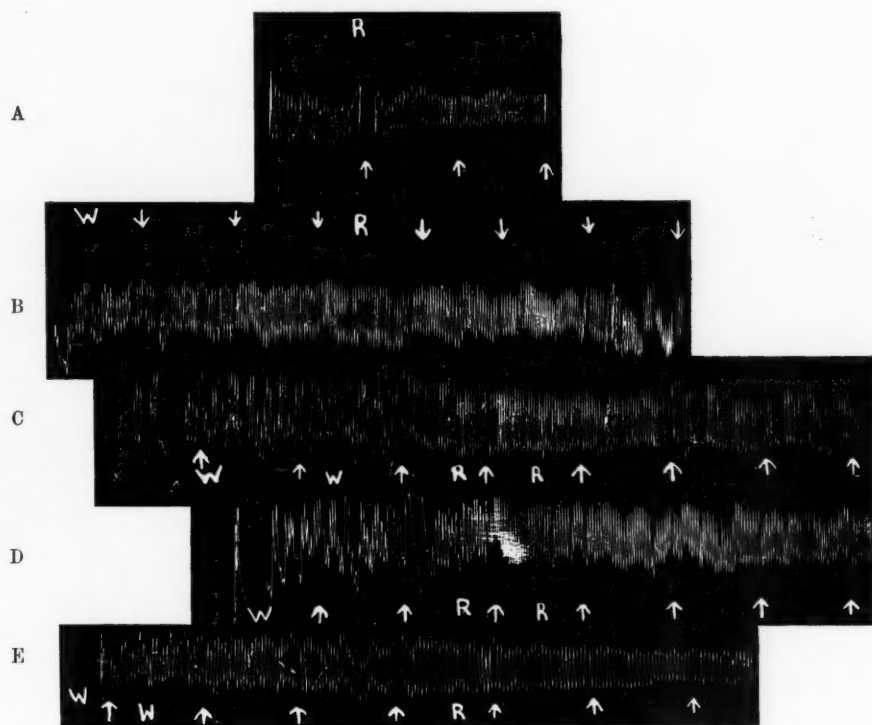


FIG. 1

Respiratory tracings of Patient C. A. At rest. B-E. During three minutes' work and subsequently. B. Before oxygen. C. Third day of oxygen treatment. D. Two days after oxygen. E. Six days after oxygen.

The white arrows indicate minutes. w indicates work, and R indicates rest.



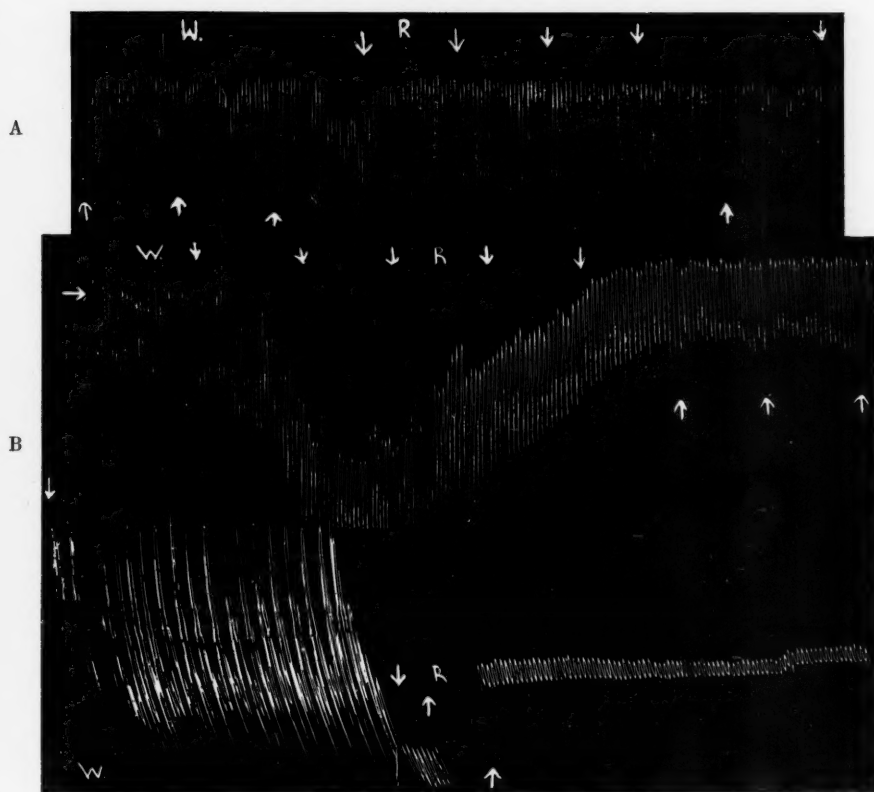
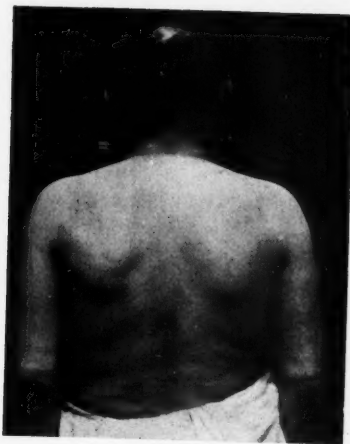
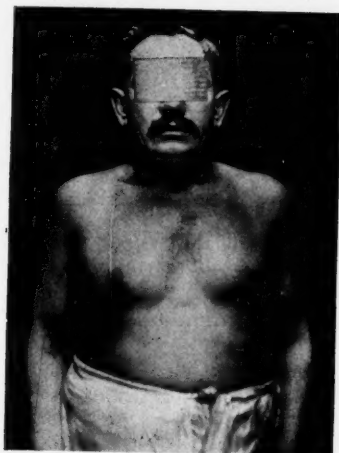


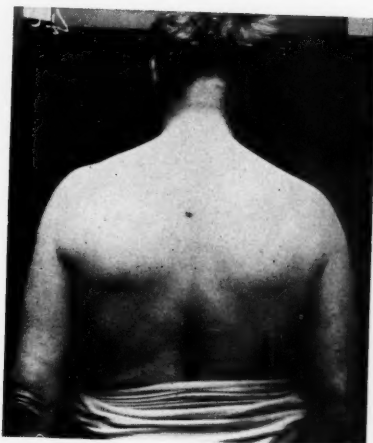
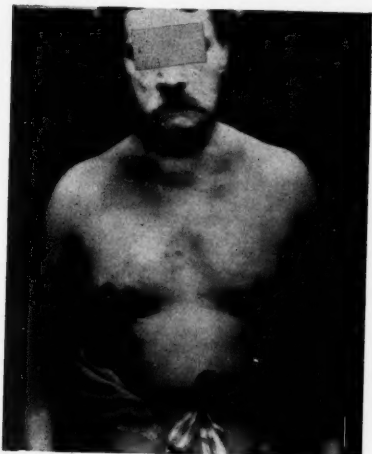
FIG. 6

Respiratory tracing of Patient M, during 3 minutes' work at 6 steps a minute and for 5 minutes afterwards. A. Third day of oxygen treatment. A very slight fall in the tracing is seen at the end of the third minute of exercise. B. Eleven days after oxygen treatment. A big fall in the tracing is seen during the second and third minutes of exercise and the first two minutes of rest. The stethographic tracing is shown beneath.

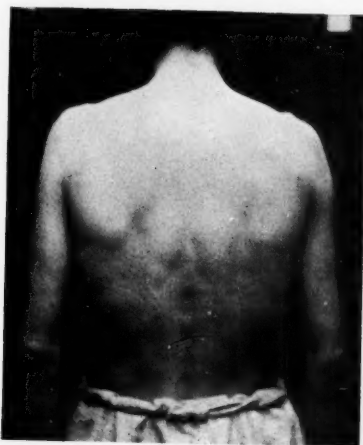
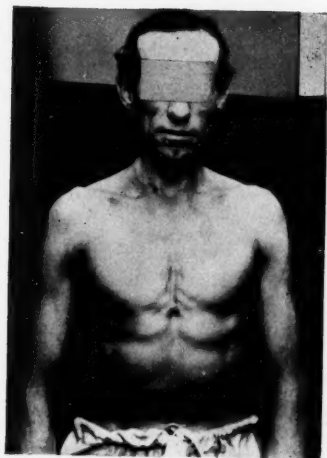
The beginning of work and minute periods through work and rest are indicated by the white arrows. W indicates work, and R indicates rest.



PATIENT C.



PATIENT M.



PATIENT G.

FIG. 7



THE MAGNESIUM CONTENT OF THE CEREBRO-SPINAL AND OTHER BODY FLUIDS¹

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THE following investigations were undertaken primarily to determine (1) the normal magnesium content of the cerebro-spinal fluid, and (2) if any variations from this normal occur in disease, especially of the nervous system.

1. *Historical.*

There are to be found in the literature but few observations on the magnesium content of cerebro-spinal fluid.

Mestrezat (1) found, in a mixture of twenty normal fluids, 0.05 gm. of MgO per litre, an amount which he thought somewhat high on account of some of the subjects having taken a magnesium saline purgative two days previous to lumbar puncture.

Barrio (2), using a modified Kramer-Tisdall method (accurate to about 0.4 mg. per 100 c.c.), in ten syphilitic fluids found amounts of magnesium varying from 1.4 to 6.1 mg. per 100 c.c.

Weston and Howard (3) estimated the magnesium content of both serum and cerebro-spinal fluid by the Kramer-Tisdall method in seventeen cases of mania and ten of melancholia. In mania they found that the limits of magnesium in both the serum and the cerebro-spinal fluid were 2.1 to 2.7 (average 2.4) mg. per 100 c.c.; in melancholia the corresponding values were, for the serum, 2.3 to 2.7 (average 2.4) mg. per 100 c.c.; for the cerebro-spinal fluid 2.3 to 2.7 (average 2.5) mg. per 100 c.c.

2. *Method.*

The method used is identical in principle with that employed in all the more recent work on magnesium in the body fluids, i. e. after the fluid has been freed from calcium, the magnesium is precipitated as MgNH_4PO_4 , and the phosphate

¹ Received July 26, 1926.

² Work carried out during tenure of a Beit Memorial Research Fellowship.

content of the precipitate having been estimated by a micro-method, the magnesium content is calculated. The method used is given in detail, since it incorporates various modifications which make it more accurate.

To 2 c.c. of serum (or cerebro-spinal fluid) in a 12 c.c. centrifuge tube of the Kramer-Tisdall type (4) add 3 c.c. of water and 1 c.c. of a saturated aqueous solution of recrystallized ammonium oxalate. Allow this to stand for one hour to ensure complete precipitation of calcium as oxalate and then centrifugalize at 3,000 R.P.M. for ten minutes. To 5 c.c. of the supernatant fluid (i.e. the equivalent of $1\frac{2}{3}$ c.c. of serum) add 3 c.c. of a mixture containing one volume of a 2 per cent. aqueous solution of acid ammonium phosphate and two volumes of redistilled ammonia. After thoroughly mixing the contents, allow the tube to stand overnight. Next morning centrifugalize at 3,000 R.P.M. for ten minutes. By careful decantation the supernatant fluid is removed without disturbing the precipitate of ammonium magnesium phosphate. The precipitate is then disturbed by tapping gently the lower end of the tube and washed by carefully pouring down the sides of the tube (taking care to wash them completely) 5 c.c. of a mixture containing two volumes of absolute alcohol and one volume of redistilled ammonia. The tube is then again centrifugalized at 3,000 R.P.M. for seven minutes. This procedure is repeated twice. After the third washing the supernatant fluid is removed by decantation and the precipitate is dissolved in 5 c.c. of 0.01 N sulphuric acid. The phosphate in this solution is then estimated by Briggs's (5) modification of the Bell-Doisy method as follows:

To the solution obtained as above, and to 5 c.c. of a standard solution of MgNH_4PO_4 (containing 0.035 mg. of magnesium, and prepared by dissolving 39.54 mg. of anhydrous ammonium magnesium phosphate in one litre of 0.01 N sulphuric acid), add:

2 c.c. of the acid molybdate solution,³

1 c.c. of a 40 per cent. solution of sodium sulphite in water, and

1 c.c. of a freshly prepared solution of hydroquinone.⁴

The tubes are allowed to stand for one hour and compared in a colorimeter. The amount of magnesium present in the serum expressed in mg. per 100 c.c. of the serum or cerebro-spinal fluid is given (1) by the formula $\frac{S}{U} \times 2.1$, where S = reading of standard, and U = reading of unknown against S , or (2) by setting the unknown solution at 21 (or 10.5) and dividing the reading of the standard against the unknown by 10 (or 5).

Using the above method the variations in duplicate estimations of serum or fluid do not exceed ± 2 per cent.

It is important to note that many of the reagents as ordinarily supplied often contain magnesium in amounts which would appreciably increase the final

³ Dissolve 25 grm. of ammonium molybdate in 300 c.c. water and then add 200 c.c. of 37.5 per cent. sulphuric acid.

⁴ Dissolve 0.5 grm. of hydroquinone in 100 c.c. water and add one drop of concentrated sulphuric acid.

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results. It was for this reason found necessary to redistil all the ammonia solution used, and to prepare pure ammonium oxalate by neutralizing a saturated solution of pure oxalic acid with redistilled ammonia: the ammonia-ammonium phosphate mixture was allowed to stand for 24 hours and filtered before use. Estimations were carried out as soon as possible after the serum had separated from the blood sample, in order to minimize any passage of magnesium from the corpuscles to serum.

The possibility has been considered that the results obtained by the above and similar methods might be too small by reason of—

1. The very slight solubility of magnesium oxalate in water; hence during the preliminary precipitation of calcium by ammonium oxalate, some magnesium oxalate might be precipitated with it.

2. Magnesium might be present in the serum or body fluids in organic combination and not completely precipitated as ammonium magnesium phosphate by the measures above detailed.

That neither of the above objections is valid is shown by the following data:

1. The solubility of magnesium oxalate in water, whilst only slight (0.309 grm. per litre, Lemarchaud (6)), is yet more than sufficient to allow all the magnesium in blood-serum to be completely in solution as magnesium oxalate. The addition of ammonium oxalate to a solution of magnesium sulphate containing 10 mg. per 100 c.c. of water gives no visible precipitate even after centrifugalization. Moreover, as is shown in Table I, very satisfactory recovery of the magnesium added to serum can be obtained by the above method.

TABLE I. *Recovery Experiments.*

Initials.	Magnesium Content of Serum.	Amount of Magnesium added.	(Results expressed in mg. of magnesium per 100 c.c. of serum.) Amount of Magnesium in Final Solution.	
			Observed.	Calculated.
H. C.	2.42	0.70	3.09	3.12
W. G.	2.71	0.35	3.03	3.06
W. C.	2.22	0.70	2.97	2.92
J. W.	2.44	0.175	2.66	2.615

2. That the whole of the magnesium present in the fluid is precipitated as ammonium magnesium phosphate is shown by control experiments on the ash of incinerated sera (Table II).

TABLE II. *Incineration Experiments.*

Initials.	(Results expressed in mg. of magnesium per 100 c.c. of serum.)	
	Direct Estimation on Serum.	Estimation on Ash of Incinerated Serum.
W. G.	2.71	2.74
H. C.	2.33	2.37

3. Results.

In eighteen cases blood was taken from the median basilic or median cephalic veins, and immediately afterwards 10 c.c. of cerebro-spinal fluid were withdrawn by lumbar puncture.

The results obtained are stated in Table III.

TABLE III. *The Magnesium Content of Serum and Cerebro-spinal Fluid.*

Case.	Initials.	Age in Years.	Diagnosis.	Magnesium Content (in mg. per 100 c.c.) of		Excess in Cerebro-spinal Fluid.
				Cerebro- spinal Fluid.	Serum.	
1	F. H.	16	Post-encephalitic Par- kinsonism	3.59	2.66	0.93
2	A. H.	26	Ménière's syndrome (labyrinthine degener- eration)	3.47	2.30	1.17
3	M. D.	48	Tabes dorsalis	3.47	2.59	0.88
4	E. H.	60	Lumbar pain (trauma)	3.42	2.94	0.48
5	R. B.	46	Tabes optica	3.39	2.82	0.57
6	J. W.	47	Disseminated sclerosis	3.39	2.44	0.95
7	R. N.	35	Post-encephalitic Par- kinsonism	3.39	2.69	0.70
8	P. C.	15	Epilepsy	3.36	2.80	0.56
9	E. L.	19	Disseminated sclerosis	3.31	2.71	0.60
10	M. G.	48	? Encephalitis	3.26	2.94	0.32
11	B. D.	36	Circumscribed serous meningitis	3.21	2.46	0.75
12	W. C.	25	Disseminated sclerosis	3.21	2.22	0.99
13	W. J.	18	Post-encephalitic Par- kinsonism	3.19	2.60	0.59
14	L. C.	46	Subacute combined sclerosis	3.17	2.31	0.86
15	H. C.	52	Dementia paralytica	3.07	2.56	0.51
16	W. G.	47	Tabes optica	3.07	2.55	0.52
17	F. H.	19	Post-encephalitic tre- mor	3.06	2.09	0.97
18	J. D.	52	Cerebral arterio-scle- rosis	3.02	2.55	0.47
Average				3.28	2.56	0.72

The striking fact which emerges from an examination of these results is that the magnesium content of the cerebro-spinal fluid is constantly higher than that of the corresponding contemporary serum by an average of 20-30 per cent. Regarding Cases 2 and 4 as normal, inasmuch as they presented no evidence of nervous disease nor of alterations in the other constituents of cerebro-spinal fluid, it will be seen that the magnesium content of the fluid is independent of age (15-60 years), of sex, and (with the exception of one type of disease to be considered later) of the pathological lesion present. The magnesium content of the cerebro-spinal fluid was found also to be independent of the Wassermann reaction in the fluid, of its cell-content, and of its protein content.

Since all other substances investigated, with the sole exception of the

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chlorine ion, are present in greater quantity in the serum than in the cerebro-spinal fluid (e.g. protein, calcium, potassium, phosphates, uric acid, urea, glucose, &c.), it is important to show that the amount of magnesium in the serum, as above estimated, truly represents the amount in the plasma *in vivo*. Otherwise, as the magnesium content of whole blood is greater than that of the cerebro-spinal fluid—e.g. in one case investigated the magnesium content of the serum and plasma was 2.75 mg. per 100 c.c., that of the whole blood was 4.24 mg. per 100 c.c.—it might be objected that *in vivo* the plasma contained more magnesium than the cerebro-spinal fluid, but during its separation a redistribution of magnesium occurred in such a way that the plasma content became less and the corpuscle content correspondingly increased. It may here be remarked that any such redistribution of magnesium between corpuscles and plasma would have to occur with great rapidity, inasmuch as the magnesium content of the plasma obtained by centrifugalizing oxalated blood immediately after withdrawal has always been found to be the same as that of the corresponding serum. Loeb, Atchley, and Palmer (7) have shown that in oedema fluids (pleural and peritoneal effusions) the concentrations of calcium, urea, glucose, sodium, HCO_3 , and non-protein nitrogen are approximately the same as in serum. Table IV shows that in the cases investigated the magnesium content of oedema fluids is slightly less than that of the corresponding serum, a fact which suggests, though it furnishes no cogent proof, that the magnesium content of the plasma *in vivo* is the same as that of the serum.

TABLE IV. *The Magnesium Content of Effusions.*

Nature of Fluid.		Magnesium Content (in mg. per 100 c.c.) of	
		Effusion.	Serum.
1. Pleural.	Tuberculous, purulent	2.05	—
2. "	Traumatic (blood-stained)	2.25	—
3. "	Pneumococcal, turbid	1.85	—
4. "	Rupture of lung abscess into pleura	2.40	—
5. Peritoneal.	Cirrhosis of liver	1.83	—
6. "	" " (85th paracentesis)	1.59	1.79
7. "	" " (86th ")	1.45	1.96
8. "	Carcinoma of pancreas	2.35	2.95

A much more striking demonstration of the conclusion that the magnesium content of the cerebro-spinal fluid is higher than that of the corresponding plasma *in vivo* is furnished by Table V, which shows that in cases of meningitis the excess of magnesium which is normally found in the cerebro-spinal fluid becomes relatively diminished.

TABLE V. *Cases of Meningitis.*

Initials.	Age in Years.	Nature of Meningitis.	Magnesium Content (in mg. per 100 c.c.) of		Excess of Magnesium in Cerebro-spinal Fluid.
			Cerebro-spinal Fluid.	Serum.	
W. B.	5	Tuberculous	2.47	2.46	+0.01
M. S.	10	"	2.03	2.65	-0.62
G. M.	1 $\frac{3}{4}$	Meningococcal	3.11	3.00	+0.11

The important bearing of this fact on the problem under investigation can be comprehended by reference to a previous paper (Cohen (8)), in which it was shown that in meningitis the chemical changes which occur in the cerebro-spinal fluid are of the following types:

1. An increasing concentration in the cerebro-spinal fluid of those substances which are normally present in greater quantity in the blood-plasma than in the fluid, e. g. protein, phosphates, cholesterol, calcium, uric acid.

2. The appearance in the cerebro-spinal fluid:

- (a) of substances which are normally present in blood but absent from the cerebro-spinal fluid, e. g. fibrinogen, bile-pigments, 'complement'.

- (b) of foreign substances injected into the blood-stream which normally do not pass into the cerebro-spinal fluid, e. g. iodides, methylene blue, fluorescein, meningococcus antibodies, salicylates.

3. A decreasing concentration in the cerebro-spinal fluid of those substances which are normally present in greater quantity in the cerebro-spinal fluid than in the plasma; to this group belongs the chlorine ion.

These changes are regarded as consequent on an increase in the permeability of the cells of the chloride plexus and cerebro-spinal vessels when these are damaged by the invading virus or toxin.

It follows that if the general law which covers these changes is true (i. e. that in meningitis the cerebro-spinal fluid tends to approximate to the blood-plasma in chemical composition), and if in the normal state the magnesium content of the cerebro-spinal fluid is greater than that of the blood-plasma *in vivo*, then in meningitis the excess of magnesium in the cerebro-spinal fluid should become less marked or disappear. The fact that this occurs in each of the three cases of meningitis investigated (Table V) furnishes therefore strong support to the view that under normal conditions, and in pathological states unattended by damage to the choroid plexus and cerebro-spinal vessels, *the magnesium content of the cerebro-spinal fluid is greater than that of the circulating plasma in vivo*. In this respect magnesium is unique amongst the metallic ions.

4. Chlorine and Magnesium.

The only other ion known to be present normally in greater amounts in the cerebro-spinal fluid than in the plasma is that of chlorine. Expressed in mg. per 100 c.c. the average amount of chlorine (stated as NaCl) present (a) in cerebro-spinal fluid is 700-760 mg., (b) in plasma is 570-640 mg.

That the greater concentrations of magnesium and chlorine in the cerebro-spinal fluid as compared with those in the blood-plasma are not interdependent, and, for example, not due to the passage of a double chloride of sodium and magnesium into the cerebro-spinal fluid, is indicated by the following observations on serous effusions. Analysis of the magnesium and chloride content of three ascitic fluids and their corresponding contemporary sera showed that whilst both the effusions and the cerebro-spinal fluid were richer in chlorides than their corres-

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ponding contemporary sera, magnesium was present in *smaller* amounts in the effusion than in the serum. Hence more chlorine, but less magnesium, is present in serous effusions than in the serum; thus the higher amount of magnesium in the cerebro-spinal fluid as compared with the amounts in the corresponding serum is independent of the higher chloride content of the cerebro-spinal fluid.

TABLE VI. *The Chloride Content of Effusions.*

Nature of Effusion.	NaCl (in mg. per 100 c.c.) in	
	Serum.	Effusion.
Ascitic (Table IV, Specimen 6)	616.6	665.4
" (" " 7)	585	632
" (" " 8)	570.4	628.9

5. *Post-mortem Changes.*

After death the alterations which occur in the chemical composition of the cerebro-spinal fluid are presumably dependent on two main factors:

1. *Autolysis of nerve tissue*, aided by the post-mortem increase of tissue acidity: this results, for example, in a rise in the inorganic phosphate and non-protein nitrogen content; in the appearance of choline in the fluid; &c.

2. *Death of the cells forming the barrier between the cerebro-spinal fluid and the blood* (the cells of the choroid plexus and of the cerebro-spinal blood-vessels). The permeability of these cells is thereby increased, and changes should be found in the composition of cerebro-spinal fluid similar to those occurring in meningitis in the case of those substances which are affected only slightly or not at all by autolysis of the nerve tissue; e.g. chlorides should be decreased, calcium increased. An investigation of the fluids obtained *post mortem* showed that the changes which occur were of the type anticipated.

TABLE VII. *Post-mortem Changes in Cerebro-spinal Fluid.*

Case.	Age in Years.	Hours after Death.	Diagnosis.	Cl (as NaCl) in mg. per 100 c.c. (Average normal = 740.)	Calcium in mg. per 100 c.c. (Average normal = 5.6.)	Fluid obtained by
1	14	48	Encephalitis periaxialis	585	8.5	Lumbar puncture
2	25	32	Epidemic encephalitis	—	11.3	"
3	62	12	Uraemia; chronic nephritis	631.8	8.0	"
4	53	20	Strangulated hernia	682.7	8.5	Cisternal puncture
5a	21	12	Mitral stenosis	555.75	8.0	"
5b	21	15	"	497.25	—	"
6	35	20	Intestinal obstruction	536.25	11.1	"
7	41	12	"	672.75	9.4	"
8	53	12	Death followed operation	604.4	—	"
9	52	14	Carcinoma of lung	546.6	8.0	"
10	50	22	Carcinoma of stomach	511.9	—	"

Table VIII shows that after death, the magnesium content of the cerebro-spinal fluid and the blood-serum is considerably increased.

TABLE VIII. *The Magnesium Content of Cerebro-spinal Fluid after Death.*

Initials.	Age in Years.	Hours after Death.	Diagnosis.	Magnesium Content (in mg. per 100 c.c.) of		Fluid obtained by
				Cerebro- spinal Fluid. (Normal Average = 3.28.)	Serum. (Normal Average = 2.56.)	
S. Y.	54	16½	Carcinoma of bladder	4.52	—	Cisternal puncture
F. G. W.	43	12½	Carcinoma of lung	3.53	—	"
P. M.	2½	19½	Pneumococcal meningitis	5.06	—	"
G. M.	1½	20	Meningococcal meningitis	3.81	4.33	Ventricular puncture
J. O.	40	26	Aplastic anaemia	5.83	7.50	Cisternal puncture

If the magnesium content of the serum remained unaffected by death it could be concluded that the rise in the cerebro-spinal fluid was due solely to some post-mortem increase in permeability of the various cells with which it is in contact, since it is known that nerve tissue is very rich in magnesium. The serum after death, however, contains an even greater quantity of magnesium than the cerebro-spinal fluid. The respective parts played therefore in the post-mortem rise in the magnesium content of cerebro-spinal fluid, on the one hand, by the nerve tissue, and on the other hand by the increased permeability of the separating membranes, cannot yet be definitely decided.

The explanation of the marked post-mortem rise in the magnesium of the serum would appear to be the post-mortem diffusion of magnesium salts into the serum from the blood corpuscles and the tissues. The red corpuscles, as shown above, contain more magnesium than the serum. If serum is allowed to stand in contact with the clot for a long period, the magnesium content of the serum rises (e. g. in one case after 72 hours' standing the magnesium content of the serum rose from 2.39 mg. to 2.86 mg. per 100 c.c.). The post-mortem rise in magnesium is, however, sometimes considerably greater than the highest magnesium content of whole blood during life. Hence it is probable that tissues, some of which contain 10-20 times the magnesium content of serum (see Table IX), are the main source of the post-mortem increase in the magnesium content of serum.

TABLE IX. *The Magnesium Content of Human Tissues* (Magnus-Levy (9)).

Mg. of Magnesium in 100 gm. of Fresh Tissue.			
1. Muscle	21.5	7. Kidney	20.7
2. Heart	17.4	8. Intestine	7.4
3. Brain	13.9	9. Pancreas	16.8
4. Lung	7.4	10. Thyroid	9.6
5. Liver	17.5	11. Testis	9.5
6. Spleen	14.2		

6. *The Effect of increasing the Magnesium Content of the Serum on the Magnesium Content of the Cerebro-spinal Fluid.*

As it is difficult to find patients with a raised magnesium content of the serum in whom lumbar puncture could be performed, experimental methods have been sought for increasing the magnesium content of the serum. Some of the conclusions drawn from this investigation have been dealt with in a previous paper (Cohen, 10).

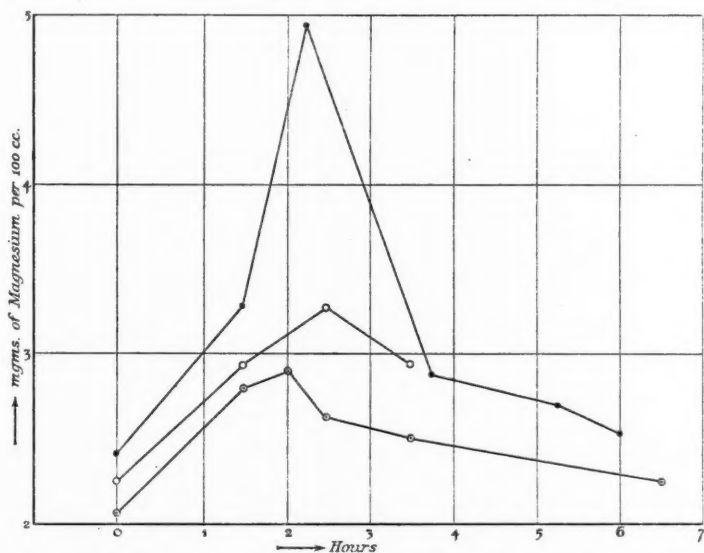


FIG. 1. Effect of intramuscular injection of $MgSO_4$ on magnesium content of serum.

For this purpose intramuscular injection was found to be most suitable, and the increase was attained by injecting 13–20 c.c. of a 10 per cent. solution of magnesium sulphate in water into the buttock. This produced a rise in the magnesium content of the serum, reaching a maximum in $1\frac{1}{2}$ – $2\frac{1}{2}$ hours after injection, and returning very nearly or completely to its original value in six hours. Fig. 1 shows three typical examples of this effect. Massage of the site of injection was found to accelerate the rate of absorption of magnesium.

Three observations were carried out on the effect of such injection on the magnesium content of the cerebro-spinal fluid. These results are detailed below and represented graphically in the accompanying figures.

Observation I. (Case A.) F. H., male, 17 years. Post-encephalitic Parkinsonism, with tremor of right upper limb (see Fig. 2).

Notes.	Time.	Time after Injection of MgSO ₄ .	Magnesium Content (in mg. per 100 c.c.) of	
			Serum.	Cerebro-spinal Fluid.
Blood taken	10.13 a.m.	—	2.66	—
C.S. F. taken (lumbar puncture)	10.15 a.m.	—	—	3.59
2 gm. of MgSO ₄ in 20 c.c. aq. injected into right buttock	10.20 a.m.	—	—	—
Blood taken	11.47 a.m.	1 hr. 27 min.	3.16	—
Blood taken (tremor much less marked)	12.15 p.m.	1 hr. 55 min.	3.44	—
Blood taken	12.45 p.m.	2 hr. 25 min.	3.07	—
Blood taken	1.5 p.m.	2 hr. 45 min.	2.69	—
C. S. F. taken (lumbar puncture)	1.30 p.m.	3 hr. 10 min.	—	3.59
Blood taken	1.45 p.m.	3 hr. 25 min.	3.13	—
Blood taken	4.30 p.m.	6 hr. 10 min.	3.02	—

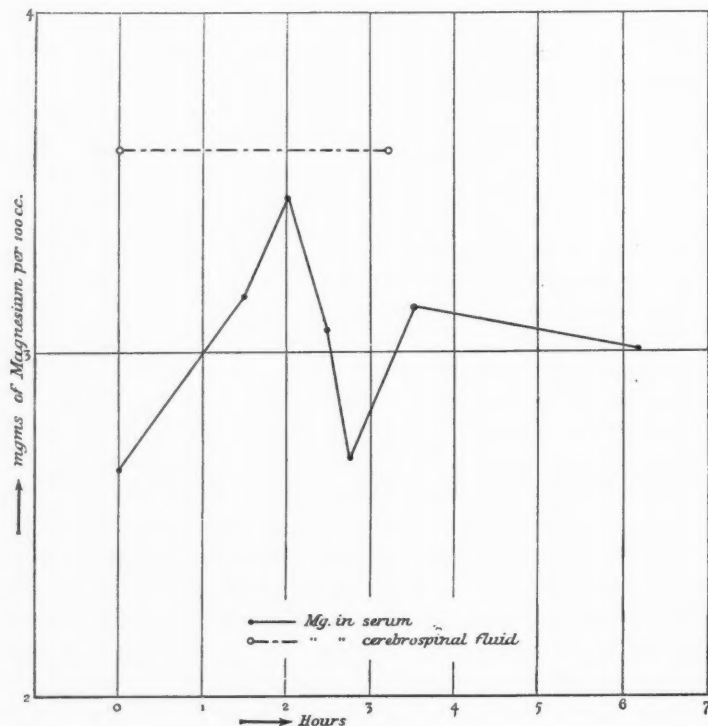


FIG. 2. Case A.

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Observation II. (Case B.) W. J., male, 18 years. Post-encephalitic Parkinsonism, with marked bradykinesia and tremor (see Fig. 3).

Notes.	Time.	Time after Injection of MgSO ₄ .	Magnesium Content (in mg. per 100 c.c.) of	
			Serum.	Cerebro-spinal Fluid.
Blood taken	10.25 a.m.	—	2.60	—
C. S. F. taken (lumbar puncture)	10.30 a.m.	—	—	3.19
2 grm. of MgSO ₄ in 20 c.c. aq. injected into right buttock and massaged	10.35 a.m.	—	—	—
Blood taken	12.5 p.m.	1 hr. 30 min.	4.24	—
Blood taken	12.35 p.m.	2 hr. 0 min.	2.88	—
Blood taken	1.10 p.m.	2 hr. 35 min.	2.90	—
Blood taken	1.28 p.m.	2 hr. 53 min.	2.90	—
C. S. F. taken (lumbar puncture)	1.30 p.m.	2 hr. 35 min.	—	3.23
Blood taken	2.10 p.m.	3 hr. 35 min.	3.44	—
Blood taken	3.7 p.m.	4 hr. 32 min.	2.88	—
Blood taken	4.35 p.m.	6 hr. 0 min.	2.64	—

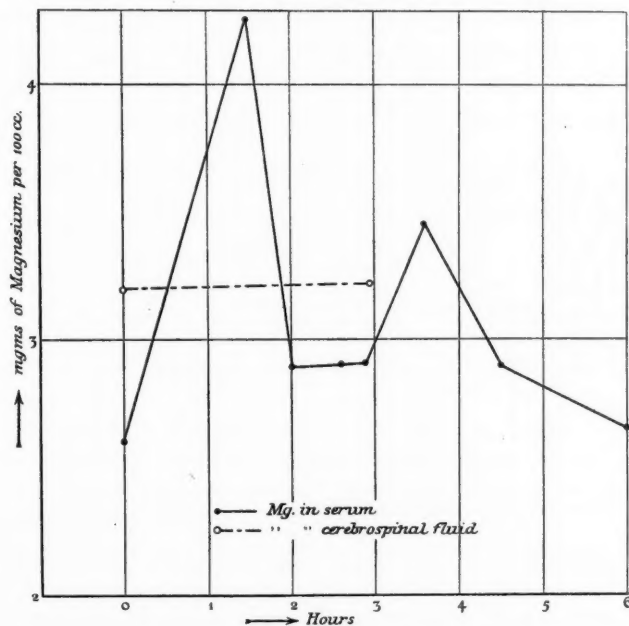


FIG. 3. Case B.

In each of the three cases detailed on pp. 182-4 it will be seen that the alterations in the magnesium content of the serum are not reflected in the cerebro-spinal fluid. The same independence was found in a case of Erb's syphilitic spinal paralysis dying from the results of an ascending pyelonephritis in which the serum was found to contain 6.27 mg. of magnesium per 100 c.c. on 22.6.25. Three days later the serum contained 6.18 mg. of magnesium, but the cerebro-spinal fluid (removed five minutes after the blood) contained only 3.29 mg. of magnesium per 100 c.c.

Observation III. (Case C.) S. M., male, 43 years. *Tabes dorsalis* with gastric crisis (see Fig. 4).

Notes.	Time.	Time after Injection of MgSO_4 .	Magnesium Content (in mg. per 100 c.c.) of	
			Serum.	Cerebro-spinal Fluid.
Blood taken	10.25 a.m.	—	2.37	—
C. S. F. taken (lumbar puncture)	10.30 a.m.	—	—	3.00
2 grm. of MgSO_4 in 20 c.c. aq. injected into right buttock and massaged	10.35 a.m.	—	—	—
Blood taken	11.35 a.m.	1 hr. 0 min.	3.28	—
Blood taken	12 noon	1 hr. 25 min.	3.16	—
C. S. F. taken (lumbar puncture)	12.5 p.m.	1 hr. 30 min.	—	3.00
Blood taken	12.35 p.m.	2 hr. 0 min.	3.18	—
Blood taken	1.35 p.m.	3 hr. 0 min.	2.78	—
C. S. F. taken (lumbar puncture)	1.40 p.m.	3 hr. 5 min.	—	3.00
Blood taken	2.15 p.m.	3 hr. 40 min.	2.76	—
Blood taken	2.32 p.m.	3 hr. 57 min.	2.74	—
Blood taken	4.30 p.m.	5 hr. 55 min.	2.86	—

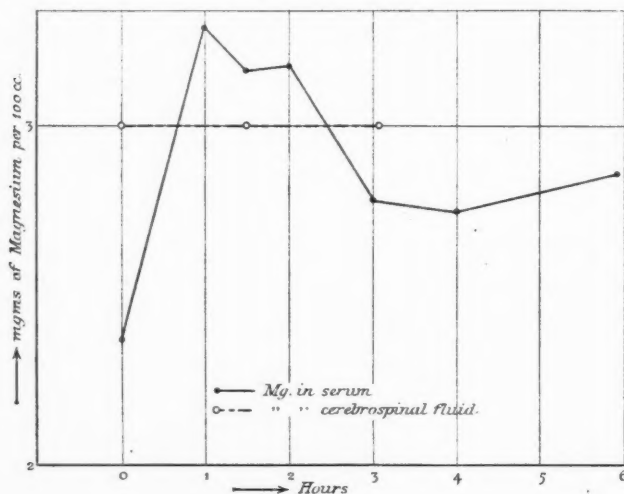


FIG. 4. Case C.

In investigating the effect of increasing the magnesium content of the serum on that of the cerebro-spinal fluid, an important difficulty arises. Whilst it is known that substances injected into the cerebro-spinal fluid are to be found within a few minutes in the blood-stream, but little knowledge exists concerning the rate of passage of substances into the cerebro-spinal fluid from the blood.

Halliday, in a recent paper (11), shows that after the oral administration of glucose the sugar content of the cerebro-spinal fluid tends to rise in about one hour. In the first and second observations recorded above, cerebro-spinal fluid was taken about one hour after the maximum rise in the magnesium content of the blood might be expected to occur as a result of intramuscular injection of

magnesium sulphate, thus allowing considerable time for any rise in the blood magnesium to affect the cerebro-spinal fluid. At this time, however, the magnesium of the serum had returned almost to its original value. It might therefore be objected that if, in the case of magnesium, any rise in the cerebro-spinal fluid closely followed that in the serum, the magnesium content of the cerebro-spinal fluid would have returned to its original value at the time the second specimen was taken.

Reference to Observation III, in which the cerebro-spinal fluid was taken $1\frac{1}{2}$ hours and 3 hours after the intramuscular injection of magnesium sulphate, shows this suggestion to be untenable. In this case, as Fig. 4 shows, the magnesium content of the serum was greater than that of the cerebro-spinal fluid for probably $1\frac{1}{2}$ to 2 hours, yet the magnesium content of the cerebro-spinal fluid before, during, and $\frac{1}{2}$ - $\frac{3}{4}$ hour after that period was the same.

From the above observations we may conclude that *the magnesium content of the cerebro-spinal fluid remains constant, in spite of a considerable rise in the magnesium content of the serum, during the period (6 hours) of our observations.*

The case of Erb's syphilitic spinal paralysis quoted above creates a very strong presumption that the magnesium of the serum may be raised for at least three days without any alteration occurring in the magnesium content of the cerebro-spinal fluid.

The remarkable rise in the magnesium content of the serum after lumbar puncture, recorded in Observations I and II, will be discussed in a separate communication.

Summary.

1. A method is described for the accurate estimation of magnesium in 2 c.c. of body fluids.

2. Observations on eighteen cases show that the magnesium content of cerebro-spinal fluid (average 3.28 mg. per 100 c.c.), in normal and pathological states other than meningitis, is constantly greater than that of the contemporary blood serum (average 2.56 mg. per 100 c.c.).

3. In meningitis the excess of magnesium in the cerebro-spinal fluid becomes less marked.

4. In pleural and peritoneal effusions the magnesium content is smaller than in the serum, although the chloride concentrations in these effusions, as also in normal cerebro-spinal fluid, are always greater than in serum.

5. The magnesium content of cerebro-spinal fluid is independent of:

- (a) Age or sex of the patient;
- (b) Cell or protein content of the fluid;
- (c) Wassermann reaction of the fluid.

6. In post-mortem specimens the serum contained more magnesium than the cerebro-spinal fluid, although there is a considerable increase in the magnesium content of both serum and fluid. The cause of these changes is discussed.

7. Experimental evidence is given suggesting that the magnesium content of the cerebro-spinal fluid remains constant in spite of a considerable increase in the magnesium content of the serum.

I desire gratefully to acknowledge the constant help given by Professor Ramsden throughout this investigation.

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INSULIN BY INUNCTION A FAILURE¹BY G. A. HARRISON²*Introductory.*

IN 1923 Telfer (4) succeeded in producing severe hypoglycaemia in fasting rabbits by rubbing insulin ointment into the shaved skin of the abdomen. In one experiment convulsive seizures occurred, and these convulsions ceased on the injection of glucose. Telfer used crude insulin, so that it is impossible to calculate the number of units employed. In two experiments he used 300 mg., and in one experiment 1,000 mg. It is probable, therefore, that the doses were enormous. In a fourth experiment 70 mg. were given, but the effect on the blood-sugar was not striking. Telfer further reports the results of subcutaneous injection of the crude product in doses varying from 27 to 160 mg. Assuming that samples of the same batch were used in the inunction and injection experiments (Telfer implies that this was the case in comparing Experiment 2 with Experiment 7), it would appear that the ratio of inunction to subcutaneous dose was of the order of 10 to 1 (compare Experiments 1 and 3 with Experiment 8). It is realized of course that such a ratio has little meaning in view of the varying rates of absorption in the two methods of administration, but it is of interest to make an approximate guess in view of the results reported in this paper. From a study of Telfer's findings it is difficult to avoid the conclusion that insulin can be absorbed through the skin if enormous doses are employed. There remains the possibility that something in the crude product other than insulin was responsible for the hypoglycaemia, but this on the face of it would appear to be extremely unlikely. The prolonged action on the blood-sugar would be expected if insulin were absorbed slowly through the skin, but the rapid fall within an hour is perhaps a little surprising.

Campbell (2) found that insulin by inunction showed a slight activity when administered in enormous doses, and states that Macleod and McCormick have duplicated Telfer's results. Woodyatt (6) obtained doubtful or frankly negative results. Campbell (2) also states: 'The procedure deserves further investigation, both as a means of prolonging the action of insulin and also as a method of producing a quite definite feeling of well-being in some patients who do not show distinct evidence of requiring insulin.'

¹ Received July 29, 1926.² Working on diabetes with a grant from the Medical Research Council.

Wallgren (5) made observations on six fasting non-diabetic children convalescent from various diseases and aged 1 to 15 years. He estimated the blood-sugar before and at hourly intervals for six hours after inunctions of insulin in doses varying from 3 to 15 units. He made control experiments, rubbing in the lanolin base without the insulin, and states that very slight or no fall in blood-sugar resulted. None the less, the fall in the blood-sugar he obtained might equally well have been due solely to the fast enforced throughout the experiment. His maximum fall (94 to 49 mg. in a child of one year) is not uncommonly encountered in children who have fasted without any insulin treatment. He claims that the baby of one year showed definite signs of hypoglycaemia, but as evidence of this he states that at first the baby struggled energetically when pricked, but that later it resisted less and less. When given glucose the baby immediately awakened and became lively. These signs can scarcely be regarded as unequivocal evidence of hypoglycaemia, and it is rare to obtain signs of a hypoglycaemic reaction in children until the blood-sugar has fallen below 50 mg. per 100 c.c. (1). Wallgren further tried insulin by inunction in a diabetic girl aged 3 years. He substituted an inunction of 20 units for a subcutaneous injection of 2 units once daily for a week, and noted that the fasting level of blood-sugar remained normal, and that the urine continued free from sugar. This, however, can scarcely be regarded as conclusive proof of the efficacy of the inunctions. The blood-sugar may very well have risen after food on the inunction days to a slightly greater height than on the injection days, without resultant glycosuria. Moreover, a dose of 2 units is relatively a small dose even for a child of only three years, and its omission would not make a great difference over a period of one week. Particularly is this so when the second subcutaneous dose of 2 units half an hour before lunch remained unaltered throughout.

Rennie (3) found that the inunction of 100 units in a human diabetic had no effect.

From this survey it may be concluded that there is definite evidence suggesting that insulin can be absorbed through the skin of rabbits when enormous doses are employed. There is no satisfactory evidence that inunctions of insulin are of any therapeutic value in human diabetes, and so far it has not really been proved that any absorption of insulin occurs through the human skin.

It is of interest to note the different bases employed in preparing the ointments. Telfer used hydrous lanolin in the first two and 'adepts preparatus' in the second two experiments. Wallgren mixed his insulin with either vaselin or lanolin. No statement as to the nature of the base employed is made in the other references quoted.

Experimental.

The experiments reported in this paper were planned primarily to decide whether insulin inunctions would be of any value in the treatment of human diabetes. It may be said at once that the conclusion reached is that they are useless as a therapeutic measure. The first observation was made on a diabetic

girl aged $2\frac{1}{2}$ years, the rest of the observations on a diabetic boy aged 11 years. The blood-sugar analyses were made by MacLean's method, and in duplicate.

Observation I. April 1924.

The patient had been on a fixed diet of 20 gm. carbohydrate, 29 gm. protein, and 43 gm. fat daily for seventeen days, without insulin. The diet was continued, but 100 units of insulin in an almond oil base³ were rubbed into the skin of the abdomen with a spatula, the inunction lasting twenty minutes. The blood-sugar was estimated at intervals:

Hours after Insulin.	Blood-sugar mg. per 100 c.c.
0	231
$3\frac{3}{4}$	249
$5\frac{3}{4}$	257
$23\frac{1}{2}$	200

The last result, 200 mg. per 100 c.c., was within the limits of variation observed at corresponding times in the previous seventeen days without insulin.

Five days later a dose of 8 units was given subcutaneously, the diet being unaltered, with the following result:

Hours after Insulin.	Blood-sugar mg. per 100 c.c.
0	152
$2\frac{1}{2}$	62
5	70

100 units by inunction therefore appeared to have little or no action on the blood-sugar, and certainly were not nearly the equivalent of 8 units by injection.

TABLE I.

Period.	Subcutaneous Insulin.		Insulin by Inunction. Morning. (Units.)	Day of Experiment.	Blood-sugar mg. per 100 c.c.	
	Morning. (Units.)	Afternoon. (Units.)			2 Hours after Insulin. 1½ Hours after Breakfast.	5 Hours after Insulin. 1½ Hours after Dinner.
(1)	5	5	0	1	61	108
				2	59	156
				8	77	181
				9	61	106
(2)	5	5	100	3	55	71
				6	77	94
(3)	5	5	0	2	79	125
				3	58	120
				8	58	111
(4)	0	5	100	1	135	122
				3	263	176
(5)	5	5	0	3	58	135

Observation II. May 1926.

A fixed daily intake of 60 gm. carbohydrate, 70 gm. protein, and 140 gm. fat was maintained throughout. On this diet, with 5 units of insulin sub-

³ Composition of base:

Almond oil	1 lb. 6 oz.
White bees-wax	3 oz.
Spermaceti	3 oz.
Distilled water	$5\frac{1}{2}$ fluid oz.

cutaneously half an hour before breakfast and another 5 units a quarter of an hour before tea, the patient's blood-sugar was kept at normal or subnormal levels throughout the day. There was never glycosuria. In fact a few extra units would easily produce definite hypoglycaemia. Thus an injection of 8 instead of the usual 5 units in the morning reduced the blood-sugar to 35 mg. per 100 c.c. in 2½ hours. The patient was in a delicately balanced state. It was therefore considered that if even a small proportion of the insulin rubbed into the skin was absorbed there would result not only lowered blood-sugars but also clinical signs of hypoglycaemic reactions. The findings may conveniently be divided into five periods (Table I).

The first was a control period showing the action of the subcutaneous insulin. In the second, 100 units by inunction were given once daily, *in addition* to the subcutaneous injections, for six days. The third was a control period. In the fourth, 100 units by inunction were *substituted* for the morning injection of 5 units. This period lasted for three days, and it will be seen at once that 100 units by inunction are not the equivalent of 5 units by injection. In the fifth period the blood-sugar rapidly returned to the usual level on the resumption of the subcutaneous injections. The insulin used in these inunctions was dissolved in a mixture of dilute alcohol and glycerol. There was never any sign of a hypoglycaemic reaction.

Observation III. June 1926.

Conditions of diet and subcutaneous injections of insulin as in Observation II. 300 units of insulin suspended in lanolin were rubbed thoroughly into the skin of the chest and of the abdomen by the patient in my presence. The inunction lasted for a quarter of an hour; the skin was then covered with jaconet for the rest of the day. Blood-sugar determinations were made at intervals after the inunction, and at corresponding times on the next day, which served as a control day, the inunction being omitted. There was no evidence of any absorption of insulin (Table II), and never a suggestion of a hypoglycaemic reaction.

TABLE II.

Time.		Blood-sugar mg. per 100 c.c.	
		Inunction Day, 2.6.26.	Control Day, 3.6.26.
11.35 a.m.	¾ hour	105	84
12.35 p.m.	1¼ hours	68	66
2.35 "	3¾ "	109	122
4.35 "	5¾ "	81	80
5.35 "	6¼ "	52	41

Insulin, 5 units subcutaneously (2 and 3.6.26) at 9.30 a.m. and 3.45 p.m., and 300 units by inunction (2.6.26) 10.50 to 11.5 a.m.

TABLE III.

Time.		Blood-sugar mg. per 100 c.c.		
		Inunction Day, 9.6.26.	First Control Day, 10.6.26.	Second Control Day, 11.6.26.
11.30 a.m.	1 hour	134	53	60
12.30 p.m.	2 hours	65	54	55
2.30 "	4 "	116	91	104
4.30 "	6 "	87	88	101
5.30 "	7 "	68	72	76

Insulin, 5 units subcutaneously at 9.30 a.m. and 3.45 p.m. each day, and 1,000 units by inunction at 10.25 to 11.25 a.m. on 9.6.26 only.

Observation IV. June 1926.

Conditions exactly as in Observation III, but 1,000 units were rubbed into the skin of the abdomen, chest, and arms (Table III). The inunction lasted for an hour. The insulin was suspended in the almond oil base, the composition of which has been given above. It will be noted that there is no suggestion of even a slow insulin action, the blood-sugar at the end of twenty-four and forty-eight hours (first estimations of control days) being no lower than usual. The first estimation on the inunction day was higher than usual. Whether this was due to the hour's exercise (vigorous rubbing) or not, it is impossible to state.

Observation V, by Dr. J. H. Burn. June 1926.

Dr. Burn, working in the Pharmacological Laboratory of the Pharmaceutical Society, very kindly tried the effect of rubbing 100 units into the shaved abdomen of each of two rabbits which had been without food overnight. The blood-sugar of these animals was estimated before and at hourly intervals for five hours after the inunction. The results were absolutely negative, there being no fall in the level of blood-sugar (Table IV). The insulin ointment was made up with lanolin and was the same as that used in Observation III. The usual fall in blood-sugar (from 152 to 58 mg. per 100 c.c.) had been obtained with 1.6 units of insulin dissolved in water and given subcutaneously to the same animal, a few days previously.

TABLE IV.

Rabbit. 3.05 kg. 100 units insulin rubbed into shaved area about three inches square.

Hours after Insulin.	Blood-sugar mg. per 100 c.c.
0	140
1	151
2	144
3	138
4	144
5	144

Discussion.

As a result of the above observations it is concluded that ointments containing insulin are useless in clinical work as a substitute for subcutaneous injection, and this is true even when large doses are administered by inunction. In Observation II, 100 units by inunction were not equal to 5 units by injection. That is to say, the ratio of inunction to injection dose exceeded 20 to 1. In Observation IV, 1,000 units by inunction failed to reduce the blood-sugar beyond the usual level, whereas on previous occasions an extra 3 units subcutaneously definitely produced hypoglycaemia (noted under Observation II). It would appear, therefore, that the ratio of inunction to injection dose exceeds 333 to 1. This point is of interest as a failure to confirm Wallgren's observations, previously referred to, from which it was suggested that a ratio of 10 to 1 was satisfactory.

In the above observations no evidence has been found in support of the absorption of insulin through the intact skin of man.

That the insulin powder used in preparing the ointments was potent is certain from the fact that it formed portion of a large batch tested and standardized in the usual way for commercial purposes. It was also independently tested by Dr. Burn, as already mentioned.

Dr. Burn's observations on rabbits gave results similar to the tests on man. The ratio of inunction to injection dose exceeded 62 to 1 (100 to 1.6) and in this respect did not confirm Telfer's findings, which give an approximate ratio of 10 to 1 according to our calculations. In fact there was no evidence of any absorption of insulin through the skin when a dose of 100 units was employed. It would therefore appear desirable to confirm Telfer's original work, putting the experiments on a quantitative basis as regards insulin dosage.

That the base in which our insulin was suspended was responsible for the negative findings seems unlikely, in view of the fact that we employed lanolin as did Telfer, and because three different bases all gave negative results.

It was intended to test Campbell's suggestion that insulin by inunction might be used as a method of producing a feeling of well-being in patients who do not show distinct evidence of requiring insulin, but in view of the complete failure to obtain any objective evidence whatever of absorption through the skin, it has been considered unsound to attempt experiments which would depend solely on the subjective sensations of patients.

Summary.

1. Inunctions of insulin are useless as a substitute for subcutaneous injection, even in large doses.
2. No evidence has been obtained that insulin can be absorbed through the intact human skin.
3. An inunction of one hundred units of insulin in lanolin did not lower the blood-sugar of fasting rabbits.

I wish to express my thanks to Dr. J. H. Burn for permission to include his experiments on rabbits; to Messrs. The British Drug Houses, Ltd., and particularly Mr. F. H. Carr, one of their directors, for their kindness in preparing and supplying the insulin ointments; and to Miss E. M. Taylor for her technical assistance.

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THE VARIABILITY OF BASAL METABOLISM¹

BY GEORGE MACFEAT WISHART

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THE utility of the basal metabolism as a diagnostic measure obviously depends on the extent to which one is justified in assuming that the normal basal metabolic rate of the healthy individual has a constant value, and that the metabolism of all healthy individuals, when due allowance is made for differences in height, weight, and age, is the same. It is doubtful if, even yet, the extent of the physiological variability, both inter- and intra-individual, is sufficiently appreciated, especially by the clinician, and, if it be appreciated at all, the observer too frequently relies on the arbitrary margin of ± 10 per cent., originally fixed by Du Bois (1) as a sure and certain dividing line between the normal and the pathological.

Harris and Benedict (2), in an extensive statistical treatment of the data for 136 men and 103 women from the Carnegie Institution Laboratory, find that, when the metabolism is expressed in calories per square metre body-surface area per hour, the inter-individual variation may be expressed by a coefficient of variation of 8.05 for males and 9.17 for female subjects.

Less prominence has been accorded to the intra-individual variation, and, in particular, to the day-to-day variation in the metabolic rate of the same individual. In this laboratory, during the last two or three years, a large number of basal metabolic observations had been made for various purposes on the same subject on consecutive days. It therefore seemed worth while to examine the variability shown in these series and compare them with the results of other workers. The data obtained indubitably show that, even under the best possible conditions of technique and co-operation of subject, fluctuations from day to day of more than 10 per cent. will not infrequently be observed in the same subject. That still greater variation must be expected in the metabolic rates of different individuals, especially where only one observation on each subject is made, will at once be evident from a comparison of the intra-individual coefficients of variation obtained in the present work with the inter-individual coefficients quoted above from Harris and Benedict.

The coefficient of variation, used throughout the present paper as a measure of variability, is the standard deviation of the series of metabolic measurements

¹ Received September 11, 1926.

expressed as a percentage of the mean of the series (in symbols: $C/V = \frac{100\sigma}{M}$).

In assessing the value of such coefficients of variation it is useful to remember that the percentage variation from the mean of the extremes of any series may be expected to fall within a value from two to three times that of the coefficient of variation.

Results of Other Workers.

In Table I are given the variations, calculated by the writer, in series of observations of the basal metabolism made by Magnus-Levy (3); Benedict and Carpenter (4); Benedict and Cathcart (5); Blunt and Dye (6); and Palmer, Means, and Gamble (7).

TABLE I.

Subject.	Coefficient of Variation of		No. of Observations.	Author.
	O ₂ Consump- tion per Min.	R. Q.		
W.	5.4	5.5	41	Magnus-Levy
H. L. H.	5.8	6.6	42	Benedict and Carpenter
L. E. E.	4.3	6.6	29	" " "
J. K. M.	4.3	5.6	28	" " "
M. A. M.	5.3	4.9	48	Benedict and Cathcart
Average of 17 female subjects	3.7	—	5 to 26	Blunt and Dye
W. W. P.	1.2	2.3	6	Palmer, Means, and Gamble

Further details concerning these series are as follows: Magnus-Levy's subject.—A male, aged 58, the observations on whom were comprised within a period of about two years. The metabolic rates reported by the author were averages in each case of three short observations.

Benedict and Carpenter's subjects.—The data were drawn from the series of short-period experiments reported in the Carnegie Institution of Washington Publication No. 261. The figures analysed were those of the largest series of single half-hourly experiments on each subject; these were chosen as being more comparable with the writer's own experiments, which were all single observations. In the case of subject H. L. H. (aged 25), the forty-two experiments extended over a period of six years; for L. E. E. (aged 31), twenty-eight of the experiments were included within three years; and for J. K. M. (aged 23), all the observations were made within practically one year. All were male subjects.

Benedict and Cathcart's subject.—A male, aged 29. Forty-seven of the forty-eight observations were made within a period of 3½ months.

Blunt and Dye's subjects.—Seventeen women varying in age from 21 to 44. The number of observations on each subject, almost all on consecutive days, varied from five to twenty-six with an average of thirteen. Each figure given by the authors was the average value obtained in two consecutive ten-minute observational periods. No measurement of the R. Q. was made.

Palmer, Means, and Gamble's subject.—A male, aged 32. Only six consecutive daily observations were made. The series is included here because of its frequent citation as evidence of the constancy of the basal metabolic rate, and for comparison with the present writer's subject, Wt.

Harris and Benedict (8) have computed the coefficients of variation in the basal metabolism (expressed in calories per square metre per hour) of eleven men investigated at the Carnegie Institution Laboratory on twenty or more occasions. The coefficients range from 2.3 to 5.3 with an average of 4.0. These values are lower than those given above for the Carnegie Institution Laboratory subjects, mainly because the metabolic values taken for analysis by Harris and Benedict are the average of several periods of observation on each day, and partly also because they refer to heat-outputs, in the calculation of which the R. Q. has been taken into account, and not to oxygen-consumption figures.

Present Observations.

The following series of observations on subjects in this laboratory were analysed by the writer:

Subject Be.—Ninety consecutive daily observations on a female subject on a fixed diet.

Subject Bu.—A male subject on whom 155 observations were made within a period of nine months. This subject subsisted on a diet of fixed calorie-content in which the form of the protein component was varied from time to time. Unfortunately these observations were not true basals in the sense that the subject was not in the post-absorptive condition, but the data have been included since all the estimations were made exactly three hours after the first meal of the day, which was always taken at the same hour, and therefore the results should be comparable within themselves.

Subject D.—Forty-three consecutive daily observations on a male subject on a fixed diet.

Subject Wn.—A male subject on whom a total of seventy-seven consecutive daily observations was made. The dietary of this subject was as follows: Twenty days on starch and olive oil, 75 gm. beef being added on three of the days; nineteen days on tapioca, cane sugar, and olive oil, gelatin being added on one of these days and egg albumin on another; nine days on a diet of bread, butter, cheese, and jam, containing 6 gm. nitrogen, gelatin and egg albumin being superimposed on one day each as before; seven days on a diet, qualitatively similar, but containing 11 gm. nitrogen, gelatin and albumin being added as before. In addition, the subject intermittently underwent several days of starvation, amounting in all to nine days. On one day, during one of the starvation periods, the subject took an amount of gelatin equivalent to that superimposed on the other diets. The remaining twelve observations were made when the subject was on his normal self-selected diet.

Subject Wt.—Nineteen observations on a male subject on a fixed diet. This

subject, during six consecutive days, endeavoured to maintain a very strict routine of life, resting during the same hours each night, eating the fixed meals at definite times, and performing, as far as possible, the same laboratory duties at the same times each day.

All the subjects were between 20 and 30 years of age.

The metabolic rates were estimated in all cases by the collection of the expired air in a Douglas bag, and analysis of an aliquot sample on the small Haldane gas-analysis apparatus. For the calculation of the heat-outputs the calorific factors of Zuntz and Loewy were used.

The results are given in Table II:

TABLE II.

<i>Metabolism in Calories per Square Metre per Hour.</i>				
Subject	Be.	Bu.	D.	Wn. ¹
No. of Observations	90	155	43	34
Arith. Mean	31.02 \pm 0.12	40.09 \pm 0.13	37.97 \pm 0.16	30.06 \pm 0.21
Coefficient Variation	5.2 \pm 0.26	5.8 \pm 0.22	4.0 \pm 0.29	5.9 \pm 0.48
Subject	Wn. ²	Wt. ¹	Wt. ²	
No. of Observations	77	6	19	
Arith. Mean	30.99 \pm 0.17	30.85 \pm 0.15	31.09 \pm 0.17	
Coefficient Variation	7.0 \pm 0.38	1.7 \pm 0.33	3.6 \pm 0.39	
<i>Oxygen Consumption in c.c.'s per Minute.</i>				
Subject	Be.	Bu.	D.	Wn. ¹
No. of Observations	90	155	43	34
Arith. Mean	176 \pm 0.69	266 \pm 0.89	222 \pm 0.98	174 \pm 1.26
Coefficient Variation	5.5 \pm 0.28	6.2 \pm 0.24	4.3 \pm 0.31	6.2 \pm 0.51
Subject	Wn. ²	Wt. ¹	Wt. ²	
No. of Observations	77	6	19	
Arith. Mean	179 \pm 0.96	198 \pm 1.07	199 \pm 1.13	
Coefficient Variation	7.0 \pm 0.38	2.0 \pm 0.39	3.7 \pm 0.40	
<i>Respiratory Quotients.</i>				
Subject	Be.	Bu.	D.	Wn. ¹
No. of Observations	90	155	43	34
Arith. Mean	0.809 \pm 0.002	0.869 \pm 0.003	0.806 \pm 0.003	0.778 \pm 0.006
Coefficient Variation	4.2 \pm 0.21	5.8 \pm 0.22	3.5 \pm 0.25	6.7 \pm 0.55
Subject	Wn. ²	Wt. ¹	Wt. ²	
No. of Observations	77	6	19	
Arith. Mean	0.791 \pm 0.005	0.813 \pm 0.005	0.803 \pm 0.006	
Coefficient Variation	7.8 \pm 0.42	2.2 \pm 0.43	4.6 \pm 0.43	

Wn.¹—Days of non-protein diet only, excluding starvation days.

Wn.²—All observations.

Wt.¹—Days of fixed routine.

Wt.²—All observations.

The following is a summary of the main features exhibited in the above table:

Remarkable similarity is shown between the variabilities here reported and those found by other workers using different methods. The day-to-day variability in both metabolism and respiratory quotient, when one observation per diem is made, may be expressed by a coefficient of variation of about four or five; this

means that, in a series of estimations, the minimum and maximum values may differ by as much as 30 per cent.

Ordinary variations in diet appear to affect the basal metabolic variability but little. Where the diet is extensively and abnormally varied, especially, as is to be expected, where the amount of protein taken fluctuates considerably, the metabolic variability is increased (Wn.²). The daily fluctuations in metabolism may be considerably diminished by living an extremely routine life (Wt.¹).

The basal metabolic variability within the individual amounts to about one-half of the inter-individual variability.

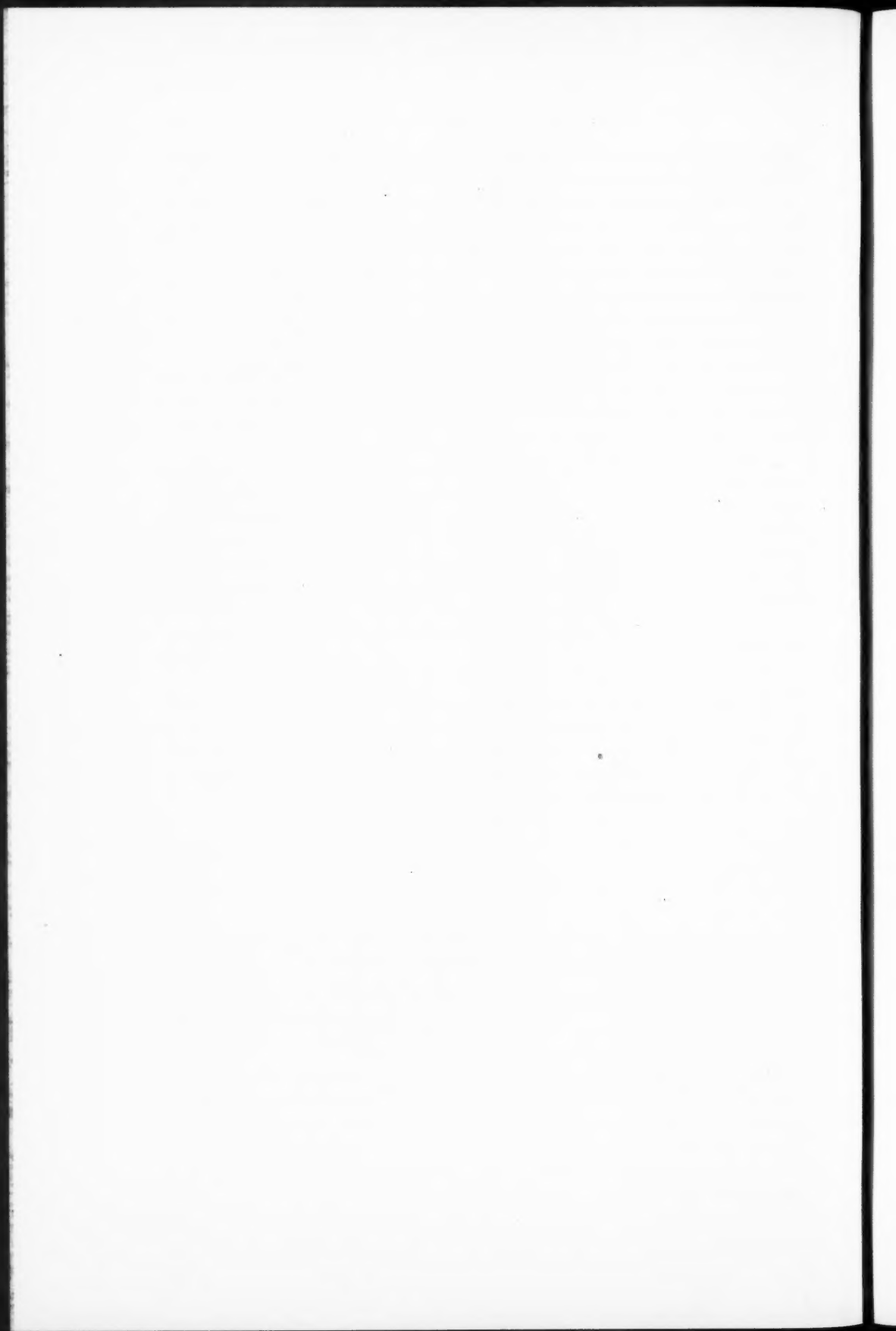
There is a remarkable similarity between the coefficient of variation of the metabolism and the coefficient of variation for the respiratory quotient in each subject. This holds even for Wn., where the R. Q. underwent abnormal fluctuations; on the starvation days the R. Q. in this subject often fell below 0.7.

As would be expected on theoretical grounds, a comparison of the variabilities of the heat-output values and the oxygen-consumption values shows that slightly more constant values are obtained when the metabolism is expressed in heat-units, in the calculation of which the value of the R. Q. has been taken into account. The only exception is to be found in the case of Wn.². This is doubtless due to the occurrence of abnormal respiratory quotients on several of the starvation days, as the smaller series for this subject, Wn.¹, from which the starvation periods are excluded, show a similar higher variability in the oxygen-consumption values.

Finally, comment may be made on the fact that of the four subjects, for whom true basal estimations are available, three showed metabolic rates considerably below Du Bois's (9) standard, Be. being - 16.2 per cent., Wn. - 21.5 per cent., and Wt. - 21.3 per cent. All these subjects were in apparently perfect health, and, apart from the above observations, have had their basal metabolism measured at various other times and by various observers, with similar low results.

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THE INFLUENCE OF PREVIOUS MUSCULAR ACTIVITY AND OTHER FACTORS ON THE BASAL METABOLISM¹

By GEORGE MACFEAT WISHART

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IN a previous paper (1), the variation exhibited in several series of consecutive daily observations of the basal metabolic rate in five different subjects was considered. As two of these subjects had on certain days, in addition to their ordinary routine activities, performed a measured amount of work on an ergometer, and a third had subsisted on distinctly abnormal diets, the data obtained have been further analysed with reference to these factors, and the results are submitted in the present paper.

Effect of Previous Muscular Work.

That the effect of muscular effort on the metabolism may persist for some considerable time after the work is ended was appreciated by Jaquet (2), who, referring to the making of physiological observations after mountain ascents, considered that at least twenty-four hours should have elapsed after the ascent before any observations were made on the climbers. Further, it is now well established that subjects accustomed to perform large amounts of muscular work frequently, such as athletes in training, have a basal metabolic rate higher than the average (Benedict and Smith (3) and others). Benedict (4) mentions the possibility of these high metabolic rates of athletes being due to the after-effects of severe muscular work. Benedict and Cathcart (5), in some of their observations on the professional cyclist, M. A. M., found that, four hours after the work period was ended, an increase in the resting metabolism of 14 to 15 per cent. over the pre-work resting value was frequently to be observed, and, in one instance, over five hours after the work was finished, the resting metabolism had not yet returned to its pre-work value.

While it thus seems that hard muscular work, undertaken an hour or two before the basal observation is made, would undoubtedly raise the result obtained for the basal metabolic rate, such observations are usually made in the morning before any undue muscular effort has been indulged in, and Benedict and Crofts (6) have shown that the ordinary activities of rising, dressing, walking a short

¹ Received September 11, 1926.

distance to the laboratory, &c., are unassociated with any disturbance of the subsequently observed basal metabolism. The question arises, however, how long the effect noted by Benedict and Cathcart (5) lasts; is the after-effect of moderate or severe muscular activity sufficiently prolonged to exert an effect on the basal metabolic rate observed on the subsequent morning? The data from two of the writer's subjects, Bu. and D., offered material for the investigation of this point.

Details concerning these subjects will be found in the previous paper. The observations on Bu. are not strictly basal, in the sense that they were not made in the post-absorptive state, but, since this subject was on a controlled diet, the meals always being taken at the same hour, and the resting metabolism observed at exactly the same time each day, the results should be comparable within themselves.

Both subjects had their basal metabolic rates determined daily, and during certain periods, each of several consecutive days, both performed 25,000 kilogram-metres of work on a hand-ergometer in exactly one hour. This amount of work was, to these individuals, a moderate but not a severe task. The mean metabolic rates for the 'work' and 'non-work' days, along with the variability of each set of observations (as expressed by the coefficient of variation), are set forth in Table I. The 'work' series include the basal observations made on the days on which work was done, with the exception of the first day of each work period plus the observation on the day immediately following the end of each work period. The 'non-work' series include the remainder of the observations.

TABLE I. *Calories per Square Metre per Hour.*

Subject Bu.	Non-work Days.	Work Days.	Difference.	Difference %.
No. of Observations	89	65	—	—
Arith. Mean	39,67 \pm 0.16	40,56 \pm 0.17	0,89	2,2
Coefficient Variation	5,6 \pm 0.28	5,5 \pm 0.32	—	—
Subject D.				
No. of Observations	22	21	—	—
Arith. Mean	37,73 \pm 0.22	38,23 \pm 0.22	0,50	1,3
Coefficient Variation	4,1 \pm 0.42	3,9 \pm 0.41	—	—

It will be seen that, in both cases, the mean metabolic rate during the work periods was slightly higher than during the non-work periods, but the difference is so slight that, in any but such long series of experiments, it would be masked by the normal variability of the metabolism.

Judged by statistical criteria, the difference in the case of Bu. was a significant one, the ratio of the actual difference of the 'work' and 'non-work' means to the probable error of the difference of these means being $\frac{0.89}{0.246}$ or 3.6. The difference found with D. (a much shorter series) is of doubtful significance, the ratio in his case being 1.6.

With regard to the qualitative character of the metabolism, Benedict and Cathcart's (5) experiments demonstrated that during the performance of the work the respiratory quotient increases above that of the pre-work resting value,

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and that after work the quotient falls, often to a value below the pre-work level. An analysis of the respiratory quotients for the 'work' and 'non-work' periods for Bu. and D. is given in Table II.

TABLE II. *Respiratory Quotients.*

Subject Bu.	Non-work Days.	Work Days.	Difference.
No. of Observations	89	65	—
Arith. Mean	0.877 ± 0.004	0.860 ± 0.004	0.017
Coefficient Variation	5.6 ± 0.28	5.6 ± 0.33	—
Subject D.			
No. of Observations	22	21	—
Arith. Mean	0.812 ± 0.003	0.799 ± 0.003	0.013
Coefficient Variation	4.0 ± 0.41	2.6 ± 0.27	—

A slightly lower respiratory quotient during the work periods is found, on the average, in both cases. The actual difference between the two mean respiratory quotients was, in Bu. 3.3 times, and in the case of D. 2.3 times, the probable error of their differences.

The after-effect of an hour's moderately severe muscular work, quantitatively, in raising the basal metabolism and, qualitatively, in altering the metabolism in the sense of a lower respiratory quotient is still in evidence on the day following the work (in the present experiments, twenty-one hours after the work was done). The differences, however (1 to 2 per cent.), are so small as to be entirely obscured in occasional observations by the normal variations in the metabolic rate, and, therefore, from the point of view of the use of metabolic measurements for diagnostic purposes, are negligible.

The coefficients of variation give little evidence that the basal metabolism is any more constant during the work periods than at other times.

Effect of Dietary Changes.

While basal metabolism is always measured in the post-absorptive condition, so as to exclude the influence of ingestion and assimilation of food, the question arises whether, in the twelve to fifteen hours allowed by the definition of basal metabolism, the body tissues have always reached a state of constant composition, irrespective of the nature of the diet.

Cathcart and Orr (7) have noted, in a normal subject, on a protein-rich diet, a metabolic rate higher than the average for the same subject on a mixed diet. On carbohydrate-rich and fat-rich diets the basal metabolism was lower than the mixed diet value. Benedict and Cathcart (5), in the experiments previously referred to, found the oxygen consumption on a carbohydrate-rich diet lower than the average, and higher than the average on a carbohydrate-poor diet. Krogh and Lindhard (8), in their paper on 'The Relative Value of Fat and Carbohydrate as Sources of Muscular Energy', stated that, on a protein-poor diet, the basal metabolism is at a minimum at respiratory quotients of intermediate value, increasing about 5 per cent. when the respiratory quotient falls to a value

indicating combustion of fat alone, and rising about 3 per cent. when the quotient reaches unity.

Two of the writer's subjects were on controlled diets, the nature of which was altered from time to time. Bu. was on a diet of fixed calorie content in which the form of the protein component was altered. It is impossible to attach too much importance to the results from this subject, as the observations, though made under strictly comparable conditions each day, were not done in the true post-absorptive condition; but it is noteworthy that the average metabolic rates are very similar, regardless of the form in which the protein was taken.

The other subject, Wn., subsisted on a series of different, and at times very abnormal, diets, the details of which have been given in the previous paper. In Table III are given the average metabolic rates, the relation of each average rate to the average of the observations on the subject's normal diet, and the variability observed in each series, expressed by the coefficient of variation.

TABLE III.

Diet.	No. of Observations.	Arith. Mean.		Relation to Normal Diet. Mean.		Coefficient Variation.	
		Metabolism. Calories per Square Metre per Hour.	R. Q.	Metabolism.	R. Q.	Metabolism.	R. Q.
All Observations	77	$30,99 \pm 0.17$	$0,79 \pm 0.005$	-0,68	+0,02	$7,0 \pm 0.38$	$7,8 \pm 0.42$
Normal Diet	12	$31,67 \pm 0.33$	$0,81 \pm 0.008$	—	—	$5,3 \pm 0.72$	$5,3 \pm 0.73$
Starch and Oil	17	$30,62 \pm 0.23$	$0,76 \pm 0.006$	-1,05	-0,05	$4,7 \pm 0.54$	$4,8 \pm 0.55$
Tapioca, Sugar, and Oil	17	$29,50 \pm 0.30$	$0,80 \pm 0.009$	-2,17	-0,01	$6,3 \pm 0.73$	$7,0 \pm 0.81$
Mixed [Low N.]	7	$30,51 \pm 0.28$	$0,86 \pm 0.012$	-1,16	+0,05	$3,6 \pm 0.65$	$5,7 \pm 1.03$
Mixed [High N.]	4	$34,58 \pm 0.38$	$0,88 \pm 0.004$	+2,91	+0,07	$3,3 \pm 0.78$	$1,3 \pm 0.31$
Starvation	9	$30,80 \pm 0.15$	$0,72 \pm 0.011$	-0,87	-0,09	$2,2 \pm 0.35$	$6,6 \pm 1.05$

As may be seen from the table, the average basal metabolic rates were not dissimilar on the different diets with two exceptions—the low figure for the tapioca, sugar, and oil period, and the high average for the high-protein period. The first was no doubt due to under-nutrition and the trying experimental conditions, as, during this time, the subject intermittently underwent four short periods of complete starvation. A point of interest is that, on the subsequent diet, the mixed low-nitrogen diet, the metabolic rate did not return to the normal diet value, although, as judged by the urinary nitrogen, the protein metabolism on each of these two diets was practically identical.

The high average observed on the mixed high-nitrogen diet is in full agreement with Cathcart and Orr's (7) finding that the stimulation of metabolism resulting from the ingestion of protein lasts for a considerable time after the actual taking of the protein. Despite the normal variability of the metabolic rate, this stimulant effect of extra protein in the diet of the previous day will, as a rule, show itself even in isolated estimations.

On examining the coefficients of variation for the longer series shown in the above table, the similarity between the variability of the metabolic rate and the variability of the respiratory quotient, which was commented on in the previous paper, is quite striking.

The data for the starvation days, which showed a respiratory quotient varying with the condition of the body's store of glycogen, are of particular interest. Despite its extensive qualitative alterations, the metabolism quantitatively exhibits a remarkable constancy; presumably the purely katabolic changes of the starving organism are more constant than the combined anabolism and katabolism, and consequent redistribution of material, in the same organism when feeding.

Regarding the effect of changes in the relative amounts of carbohydrate and fat in the diet, little can be said from the observations on Wn., as, excluding the starvation periods, the carbohydrate intake varied only from 320 to 370 gm. per day and the fat-intake from 84 to 112 gm. per day.

Relation of the Basal Metabolic Rate to the Endogenous Metabolism.

In 1914 Palmer, Means, and Gamble (9), considering that the creatinine excretion might be taken as an indicator of the active protoplasmic mass of the individual, compared the basal metabolic rates of a number of subjects with their daily creatinine elimination. Cathcart (10), in an address to the British Medical Association, commenting on the indications of a difference in metabolic nature between muscular contraction and muscular tonus, suggested that basal metabolism may be, in large part, the expression of the metabolism of tonus. After prolonged voluntary tonic contraction, Pekelharing (11) has demonstrated an increased excretion of creatinine and, under similar circumstances, Cathcart and Leathes (12) and Leathes and Orr (13) have shown an increased output of both creatinine and uric acid.

In view of such findings, it seemed worth while to compare, in this subject, Wn., the relationship between the metabolic rate and the total nitrogen excretion with the relationship between the metabolic rate and the excretion of nitrogen in one of its endogenous forms. Unfortunately, the daily excretion of the most characteristic endogenous product, creatinine, was not investigated, but daily estimations had been made of the uric acid output. In this subject, as the diets were almost entirely purine free, the uric acid excretion was probably as good an index of the endogenous metabolism.

Table IV gives the coefficient of correlation (r) between basal metabolism and daily excretion of total nitrogen along with that between basal metabolism and uric acid output.

TABLE IV.

	Between Total Urinary Nitrogen and Basal Metabolism.	Between Uric Acid Output and Basal Metabolism.
Coefficient of Correlation r	$+0.70 \pm 0.05$	$+0.62 \pm 0.06$

The values show a significant correlation in both cases, but are more in favour of a relationship between the basal heat-output and the nitrogenous metabolism as a whole, than between heat elimination and the endogenous nitrogen metabolism, as expressed by the uric acid output.

Summary.

The performance of one hour's moderately severe muscular work causes an average increase in the basal metabolic rate of the following day of about 1 to 2 per cent. The respiratory quotient is also slightly lowered by work on the previous day. The differences are so small, however, in comparison with the normal variability of the metabolism, as to be demonstrable only in the averages of long series of observations.

The daily performance of this work had no effect in diminishing the day-to-day variability of the metabolic rate.

In contrast with the slight effect of work, a high-protein diet on one day will quite markedly raise the basal metabolic rate of the subsequent day. This increase is great enough to be evident, as a rule, even in isolated observations. A fairly high correlation coefficient (0.7) between the total nitrogen excretion and the basal metabolic rate was found in a subject whose dietary was extensively varied in the amount of its protein component.

During the first days of starvation, despite the rapidly falling respiratory quotient, the variations from day to day in the basal metabolic rate were abnormally small.

A closer correlation was found between the basal metabolic rate and the total nitrogen excretion than between metabolic rate and uric acid excretion.

It is a pleasure to record my indebtedness to Professor E. P. Cathcart for his helpful advice and criticism, and to those members of the laboratory staff who acted as subjects or gave me access to their results.

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THE RELATION OF PULSE-RATE TO TEMPERATURE IN FEBRILE CONDITIONS¹

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It has long been recognized that an increase in body temperature is accompanied by a rise in the pulse-rate, the relationship being found both in the clinic (1, 2) and under experimental conditions (3). Most writers speak of a general correspondence between the increase in pulse-rate and the elevation in temperature. Mackenzie (4), however, has noted that in the more simple febrile affections there is, roughly speaking, an increase of 8-10 beats for each 1° F. rise in temperature. Further, he observes that this rule does not hold universally, but that any considerable departure from it should always arouse watchfulness and suggest the possibility of the presence of other complications.

The increased pulse-rate in fevers has been regarded by many as evidence that the heart was directly involved, and in consequence much attention has been directed to this organ in febrile conditions. On the other hand, so long ago as 1871, Liebermeister (2) suggested that the rapid pulse in such cases was merely a passive consequence of the rise in temperature. Many chemical and physical changes are hastened in this way as the temperature is raised, and physiological processes, such as ferment action, phagocytosis, tissue oxidation (5), and metabolism, behave in the same fashion. Gaskell (3) showed that this was also true of the heart, for by applying heat directly to the region of the frog's sinus a marked increase in the rate of the heart rhythm resulted. The application of cold produced an opposite effect. The question as to whether the pulse acceleration in fevers is due to a local action on the heart or is merely a consequence of the rise in body temperature is an important one, since its answer determines both prognosis and treatment.

My attention was particularly drawn to the subject by the chart reproduced in Fig. 1, where the curious movements of the temperature records are closely copied by the pulse-rate. The striking resemblance between the two curves suggested a relationship other than chance, and stimulated investigation. An examination of the figures from this case of pneumonia showed that a high degree of correspondence existed between the pulse and the temperature, as may be seen from the lines which are calculated respectively from the observed pulse

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and temperature values. For the analysis, figures up to the seventh day were employed, since beyond this point the pulse-rate appeared to drop rather rapidly under the action of digitalis. In the later part of the chart the pulse runs at a level about 25-30 beats lower than the calculated values, but continues to show some correspondence with the variations in temperature.

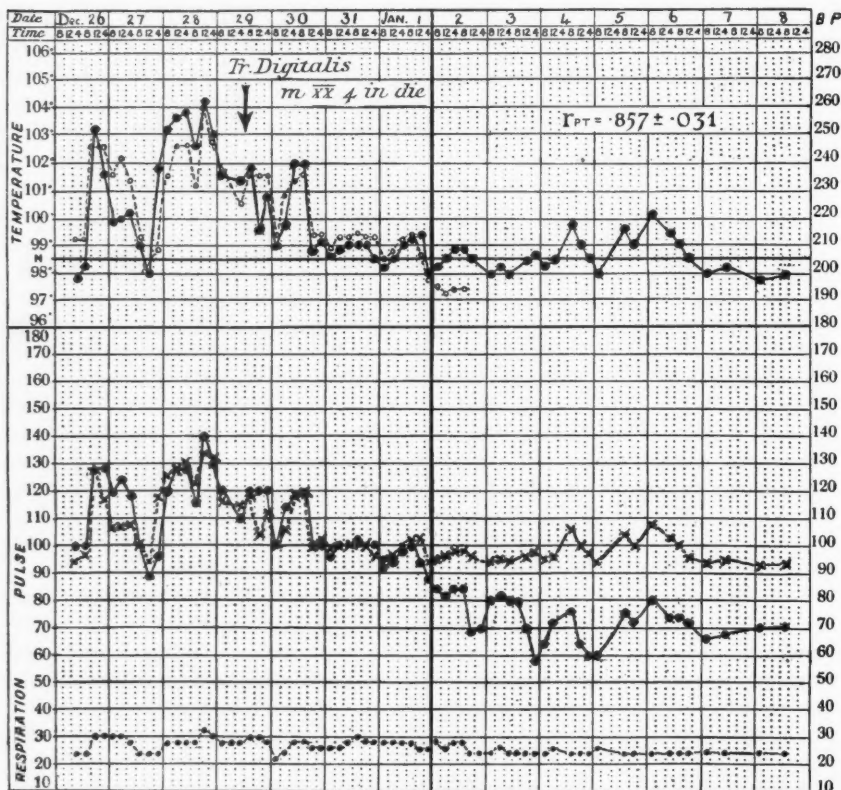


FIG. 1. Temperature chart from pneumonia patient No. 16

Observed temperature and pulse readings are shown thus: —●—.

The superimposed lines have been constructed from the formulae:

$$T = cP + d \quad \text{---} \circ \text{---} \circ \text{---} \circ$$

$$P = aT + b \quad \text{---} x \text{---} x \text{---} x$$

The figures for only the first seven days were used in the calculation. Digitalis was commenced on the fourth day and begins to show its effect on the eighth day, and the observed pulse thereafter runs from 20 to 30 beats lower than the calculated figures.

Material and Methods.

In order to obtain further evidence of the influence of temperature on the pulse-rate, some pneumonia case-records were chosen from a large number available. At first a rough selection was made of those in which a correspondence

seemed likely; later, others were taken at random. The investigation was then extended to cases of other febrile diseases, and a comparison was made with the changes produced artificially by intravenous injections of peptone. Six non-febrile records were examined as controls. The results of these analyses are collected in Tables I, II, and III. In addition to twenty-one cases of lobar pneumonia (five of which were fatal) there were examined the records of five cases of broncho-pneumonia, four of rheumatic fever, two of tonsillitis, two of typhoid, and one each of the following: acute bronchitis, diphtheria, acute phthisis, pyelitis, and pyonephrosis. In all, there are included examples of eleven different kinds of febrile disease.

The data from each patient have been plotted graphically as in Fig. 2. A rough linear arrangement is readily seen. In order to measure the relationship between the two variables, temperature and pulse-rate, the coefficient of corre-

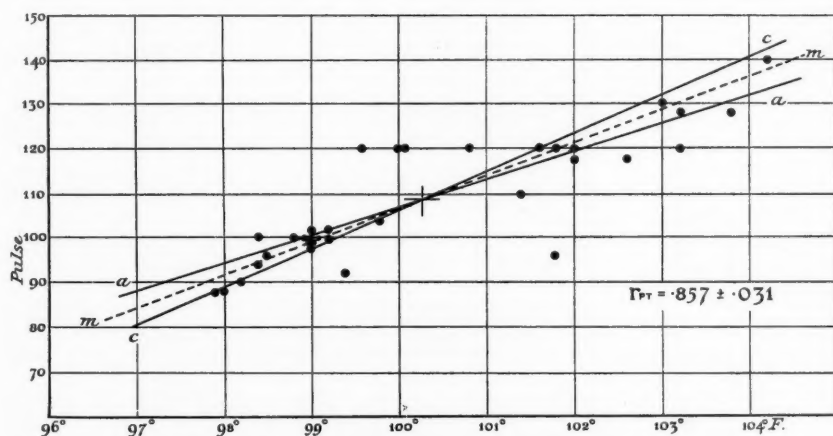


FIG. 2. Pulse-rate values for first seven days from Case 16 plotted against simultaneous temperature readings.

lation (r) has been estimated for each case *separately*. It will be recalled that a perfect positive agreement (both variables increasing together) is indicated by the figure $+1.000$, while a complete absence of relationship is shown by zero. When one variable increases as the other diminishes a perfect negative correlation is shown by the sign -1.000 . Fractions greater than 0.200 suggest a significant relationship, provided that the figure is at least four times its probable error. Values above 0.600 indicate a considerable measure of agreement. The material in each table has been arranged in order of magnitude of the respective correlation coefficients.

Some controversy has taken place as to the kind of mathematical expression which best describes the relationship of pulse to temperature. Liebermeister (2) and Lauder Brunton (6) believe that the temperature effect is greater in the higher ranges. Flatow (7), Snyder (8), and Frank (9) state that the agreement is non-linear, while Clark (10), confirming this, added that it was not a simple

TABLE I.

Group A.

Case No.	Sex.	Age.	Disease.	$T^{\circ}F^{\circ}T. \pm Ex.$	c.	c ¹ .	a.	m.	No. of Observations.	No. of Observations over 99° F.	Range of Temperature.	Drugs.	Remarks.
1.	F	25	Pneumonia	0.968 0.006	0.0623	16.05	15.11	15.62	53	29	5.6	D	
2.	F	43	"	0.960 0.008	0.1218	8.20	7.57	7.86	43	15	6.4	—	Febrile
3a.	F	36	"	0.956 0.009	0.0708	14.12	10.10	12.00	28	14	5.4	—	All figures
3b.	—	—	—	0.901 0.016	0.0782	12.79	10.38	11.50	60	14	6.6	—	Rising figures
4a.	F	20	Pyonephrosis	0.952 0.002	0.0667	14.99	13.50	14.00	10	4	4.0	—	Falling figures
4b.	—	—	—	(0.772 0.090)	0.0464	21.55	13.00	16.71	10	0	1.6	—	All figures
4c.	—	—	—	(0.654 0.086)	0.0462	21.65	9.79	15.25	20	4	4.0	—	
5.	M	13	Pneumonia	0.947 0.010	0.1144	8.74	7.83	8.22	52	23	8.0	—	
6.	M	15	"	0.926 0.024	0.1039	9.61	8.23	9.00	21	4	6.4	—	
7.	F	11	"	0.924 0.015	0.1056	9.57	8.08	8.67	43	21	8.0	—	
8.	M	10	"	0.921 0.013	0.0757	13.21	11.19	12.12	58	31	8.0	D	
9a.	F	29	Rheumatic fever	0.913 0.010	0.1390	7.19	6.26	6.75	33	17	6.4	S	All figures
9b.	—	—	—	0.828 0.031	0.0880	11.36	7.83	9.10	14	14	3.2	S	Figures 100 +
10.	M	40	Pneumonia	0.894 0.021	0.1125	8.89	7.30	8.12	40	23	6.0	—	
11.	F	25	"	0.893 0.020	0.0994	10.06	8.02	8.93	47	10	6.4	—	
12.	M	22	Typhus	0.888 0.032	0.1690	5.32	4.64	5.25	20	15	7.8	—	
13.	M	14	Tonsillitis	0.882 0.027	0.0723	13.83	10.67	12.33	75	33	6.4	—	
14.	M	23	Pneumonia	0.870 0.030	0.0697	14.35	11.40	12.75	90	9	4.6	D	Nephritic
15.	M	48	"	0.867 0.029	0.0981	10.19	7.67	8.83	33	21	5.2	D	
16.	F	29	"	0.857 0.031	0.1170	8.55	6.26	7.55	34	20	6.2	D	
17.	M	53	"	0.844 0.025	0.1225	8.16	5.81	6.88	63	19	7.2	D	
18.	M	1	Diphtheria	0.839 0.060	0.1026	9.75	6.84	8.15	11	5	6.4	D	
19.	F	47	Pneumonia	0.832 0.031	0.1047	9.65	6.60	7.93	45	20	5.0	D	
20.	F	16	"	0.813 0.036	0.0947	10.56	6.98	8.63	41	23	6.8	—	
Group B.													
21.	F	38	Tonsillitis	0.783 0.030	0.0695	14.39	8.81	11.33	74	40	7.2	D	
22.	F	23	Broncho-pneumonia	0.779 0.044	0.1089	9.79	5.81	7.71	31	15	5.8	S	Nephritic (fatal)
23.	M	39	"	0.770 0.039	0.0782	12.79	8.89	10.77	50	39	8.0	—	

24.	F	67	"	0.763	0.047	0.1021	9.81	5.66	7.50	36	24	5.4	Falling figures
4b.	F	20	Pyonephrosis	0.772	0.090	0.0464	21.55	13.00	16.71	10	—	—	
25.	F	22	Rheumatic fever	0.750	0.051	0.0811	12.83	7.00	9.50	34	21	3.8	S
26.	F	22	"	0.680	0.046	0.0492	20.33	9.62	14.50	61	3	3.2	S
27.	M	5	Broncho-pneumonia	0.671	0.043	0.0624	16.03	7.21	11.00	68	37	6.4	
4c.	F	20	Pyonephrosis	0.654	0.086	0.0462	21.65	9.79	15.25	20	4	—	All figures
28.	M	30	Typhoid	0.667	0.059	0.1141	8.76	3.83	6.05	63	58	6.6	
29.	M	27	"	0.650	0.065	0.1227	8.15	3.49	5.63	36	21	6.6	
30.	F	64	Acute bronchitis	0.634	0.147	0.0919	10.88	4.30	6.67	52	28	4.8	Asthmatic
Group C.													
31a.	M	34	Pneumonia	0.619	0.070	0.0390	25.64	9.86	15.00	35	35	3.4	(Fatal)
31b.	—	—	"	0.568	0.012	0.0925	10.81	3.49	6.44	14	14	2.6	Last 2 days
31c.	—	—	"	0.228	0.014	0.0553	18.08	4.78	9.33	21	21	3.2	First 4 days
32.	F	51	Pyelitis	0.569	0.073	0.0927	10.79	3.48	6.56	39	15	5.0	Jaundice
33a.	F	17	Acute pathisis	0.589	0.073	0.1051	9.51	2.77	6.71	56	52	4.4	Less initial figures
33b.	—	—	"	0.457	0.115	0.0768	13.02	2.90	5.75	68	59	5.4	All figures
34.	F	42	Pneumonia	0.484	0.070	0.0474	21.10	4.92	10.17	54	11	4.2	(Fatal)
35.	F	45	"	0.425	0.127*	0.0396	25.25	4.53	10.41	19	16	5.8	(Fatal)
36.	F	43	"	0.404	0.111*	0.0335	29.85	4.86	11.30	26	17	5.4	(Fatal)
37.	F	25	Rheumatic fever	0.352	0.071	0.0328	30.49	3.79	10.33	70	70	5.8	Ice-packs, &c.
38.	F	42	Broncho-pneumonia	0.335	0.109*	0.0326	30.67	3.49	10.00	30	30	6.6	Alcoholic (fatal)
39.	M	12	"	0.189	0.097*	0.0168	60.24	1.60	10.00	46	18	5.4	(Fatal)
40.	F	14	Pneumonia	0.137	0.103*	0.0166	—	1.18	—	41	41	4.8	(Fatal)
Group D.													
41.	F	30	Disseminated sclerosis	0.534	0.067	0.0279	35.84	10.25	17.50	52	—	2	
42.	F	18	Exophthalmic goitre	0.499	0.066	0.0277	36.10	9.93	14.50	59	3	3	
43.	M	63	Sciatica	0.320	0.084	0.0184	54.35	5.50	13.50	52	—	1.8	S
44.	F	47	Constipation	0.200	0.060*	0.0154	64.94	2.60	11.00	45	2	2	
45.	F	30	Exophthalmic goitre	0.003	0.114*	0.0187	—	0.926	—	35	—	2	
46.	F	55	Constipation	0.021	0.099*	0.0126	—	0.400	—	46	—	1.8	
Whit-	M	21-84	Criminals	0.288	0.020	0.0127	79.00	6.56	21.00	927	70	3.4	

* Note that in these cases the value of \bar{P} is less than four times its probable error.

TABLE III.
Group E.

Case No.	Sex.	Age.	Disease.	No. of 'Shocks'.	$T_{PT} \pm E_r$.	c.	c ¹ .	a.	m.	No. of Observations.	No. of Readings over 99° F.	Range of Temperature.	Drugs.	Remarks.
47a.	M	57	Rheumatoid arthritis	1	0.987	0.001	0.0838	11.93	11.62	11.86	3	3.9	—	
47b.	—	—	—	1	0.974	0.014	0.0794	12.59	11.91	12.12	4	3.5	—	
47c.	—	—	—	1	0.972	0.015	0.0918	10.89	10.30	10.62	5	5.7	—	
47d.	—	—	—	3	0.948	0.016	0.0842	11.88	11.17	11.50	11	6.0	—	
47e.	—	—	—	6	0.851	0.023	0.0875	11.43	8.27	9.75	18	6.8	—	
48a.	F	24	"	1	0.979	0.012	0.0647	15.46	14.81	15.14	4	3.2	—	
48b.	—	—	—	8	0.947	0.007	0.0737	13.57	12.18	12.88	22	9.0	—	
48c.	—	—	—	1	0.935	0.033	0.0824	12.14	10.61	11.50	5	6.0	—	
48d.	—	—	—	1	0.905	0.050	0.0801	12.48	10.23	11.25	2	3.5	—	
48e.	—	—	—	5	0.873	0.028	0.0845	11.83	9.00	10.38	32	19	—	
48f.	—	—	—	1	0.870	0.058	0.1210	8.26	6.21	7.12	8	6.2	—	
48g.	—	—	—	1	0.864	0.070	0.1249	8.00	5.97	6.88	6	4.2	—	
49a.	F	28	Epilepsy	1	0.974	0.014	0.0869	11.51	10.93	11.25	5	3.4	—	
49b.	—	—	—	6	(0.792	0.036	0.0579	17.27	10.82	13.89	48	9	—	
50.	F	72	Rheumatoid arthritis	2	0.955	0.001	0.1764	5.67	5.02	5.33	21	4	S	<i>B. coli</i>
51.	M	53	"	1	0.928	0.024	0.1197	8.35	10.42	9.29	15	5	—	
52.	M	12	Chronic lymphangitis	5	0.909	0.018	0.0864	11.57	9.56	10.67	61	22	—	
53a.	M	44	Rheumatoid arthritis	6	0.898	0.014	0.1084	9.22	7.41	8.33	82	42	S	<i>B. coli</i>
53b.	—	—	—	1	0.895	0.032	0.1180	8.48	6.78	7.56	17	11	—	
54.	F	41	"	5	0.877	0.025	0.0523	19.12	14.86	16.75	40	6	—	
55.	F	27	Asthma.	7	0.837	0.028	0.0884	11.31	7.92	9.50	54	10	A	
56.	F	28	Rheumatic fever	3	0.820	0.026	0.0739	13.53	9.13	11.00	22	5.6	S	Also spontaneous relapse
49b.	F	28	Epilepsy	6	0.792	0.036	0.0579	17.27	10.82	13.89	48	9	—	
57.	F	48	Rheumatoid arthritis	4	0.730	0.049	0.0876	11.42	6.07	8.33	42	7	—	
58.	F	27	Asthma	8	0.677	0.044	0.0646	15.48	7.09	10.50	68	11	A	
59.	F	33	—	2	0.662	0.079	0.0530	18.87	8.26	12.10	23	4	A	

38 observations
are below 98°
F.*B. coli**B. coli*Also spontane-
ous relapse

log. function. Re-examination of their figures shows a fairly close approximation to a linear form over the wide range of temperature likely to be met with in the living animal. Low temperatures (under 25° C.) inhibit the heart altogether, while extremes of heat beyond 40° C. produce irregularities and weakness. Knowlton and Starling (11), on the other hand, found that throughout the range from 26° to 40° C. each increase or decrease of temperature produced a uniform change in pulse-rate. From the present investigation, owing to the 'scatter' and to the discontinuous character of the observations in many instances, it is not possible to state categorically whether or not the relationship between pulse-rate and temperature is a linear function. For normal and febrile temperatures likely to be met with a straight line formula would appear to fit the facts as well as any other. Assuming such a relationship, the most probable value of pulse-

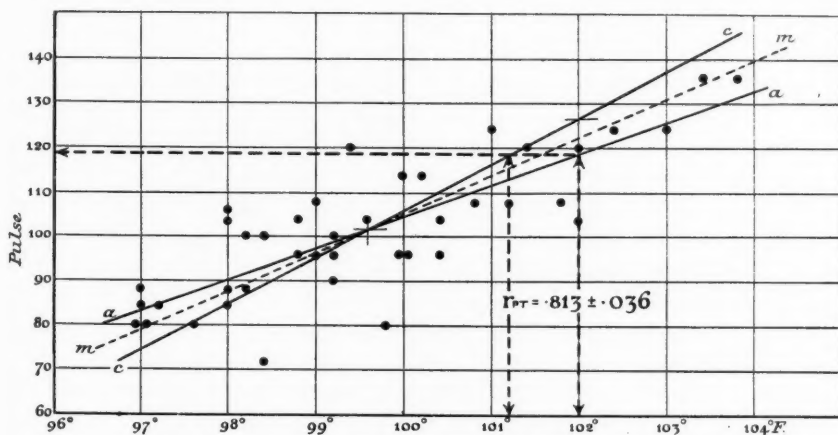


FIG. 3. Data from Case 20. The meanings of the additional lines are explained in the text.

rate for each point of temperature, and of temperature for each given pulse-rate, are obtained from the following equations:

$$\begin{aligned} P &= aT + b \\ T &= cP + d \end{aligned}$$

P and T are pulse-rate and temperature respectively, while a , b , c , and d are constants. These two formulae yield two so-called 'regression lines', whose position relative to each other depends upon the magnitude of the correlation constant, r_{TP} , that is, on the degree of relationship between the variables. Where the correlation is perfect the two lines coincide, and where the relationship is zero the regression lines are at right angles to each other.

Consider Fig. 3. The line 'a' constructed from the formula $P = aT + b$ gives, from the data available, the most probable value of the pulse-rate for each degree of temperature (e.g. pulse 119 for a temperature of 102°). It does not necessarily follow, however, that the abscissal reading of 102° F. is the best figure for a pulse of 119. This latter value would be calculated from the formula

$T = cP + d$ (line c), and it will be seen that corresponding to a pulse of 119 the most probable temperature would be 101.2°F . Both lines, then, give a 'best value' relationship between the two variables, which, read from the graph, might be expressed in terms of either variable. For example, corresponding to the temperature 102° , the two regression lines show values of 119 and 126. This appears rather anomalous, and it would seem that some intermediate value of the two readings would give a closer approximation to the true relationship, which has simply been obscured by other factors in operation. An attempt has therefore been made to get over this difficulty. Since the two regression lines approach and finally coincide as the correlation rises, it has been assumed that a line drawn midway between them would give the optimum relation between the variables. The slope of this line has been calculated for each case separately, and also for the various groups, the results being shown in column ' m ' of the tables

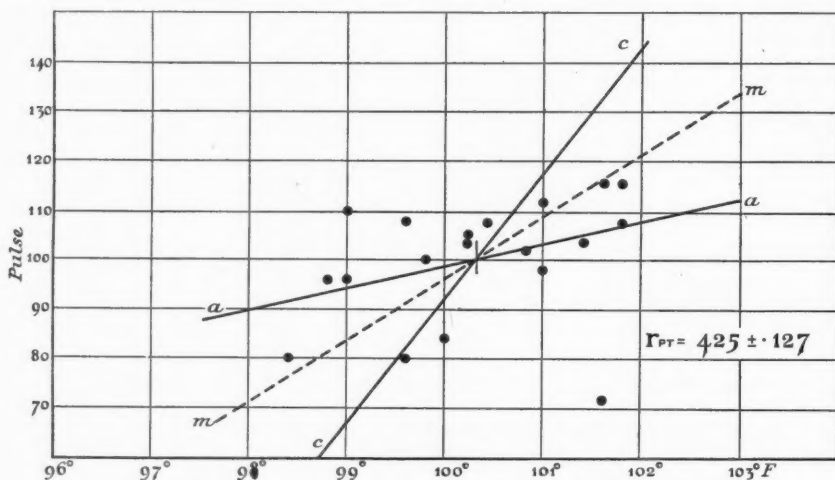


FIG. 4. Figures from a patient with pneumonia, to show the wide scatter and the poor agreement found in fatal cases.

in terms of pulse-rate per degree of temperature. These figures are not the same as the average of the values in columns ' c^1 ' and ' a '. Where the correlation is good (as in Groups A and E) little difference exists between the values of c^1 , a , and m .

In the accompanying tables (pp. 208-10 and 215) columns ' c ' and ' a ' show respectively the values of the constants c and a in the two regression formulae. Column ' c^1 ' is derived from the same regression line as column ' c ', but the value is expressed in terms of pulse instead of temperature in order to make it comparable with column ' a '. The figures in column ' m ' are taken from the middle line described above. The remaining columns are self-explanatory. The age and sex of the patient are shown, together with the disease or disorder present. Additional information tabulated includes the number of pairs of observations made use of in the calculation, the number of these in which the temperature was higher than 99°F ., and the range over which the observed temperatures extended.

The Relationship between Pulse-rate and Temperature in Health.

Biometricians have given a certain amount of attention to this subject, but the results have not been striking. In a group of normal persons a wide difference in pulse values is to be found, and the same is true of the body temperature. Many other factors besides temperature are known to influence the pulse-rate, and the relative importance of these will vary from case to case, and possibly also from time to time, in the same individual. Such factors include age, exercise, posture, mental effort, excitement and other emotions, vagal and sympathetic stimuli, peripheral resistance, the reaction of the blood, and so forth. These influences, acting in varying proportion and degree, will cause a 'scatter' which must tend to obscure the effect of temperature (see Fig. 5). If sufficient observations over a wider range of temperature are available, the influence of the latter will become more apparent (compare Fig. 6).

Miss Whiting (12), in the course of a statistical survey of anthropometric characters in a prison community, has estimated the correlation between pulse and temperature from 927 pairs of observations made on 500 individuals. The mean temperature is given as $97.373^{\circ} \pm 0.011^{\circ}$ with a standard deviation of $0.486^{\circ} \pm 0.008^{\circ}$, while the mean pulse-rate is 74.215 ± 0.245 , the standard deviation being 11.062 ± 0.173 . The crude correlation between these two variables is $+0.288 \pm 0.020$, while when corrected for age and weight, or for age and height, slightly higher values are obtained. The regression formulae are $T = 0.01266^{\circ} P + 97.4336$, and $P = 6.5551 T - 570.6300^{\circ}$, that is, the pulse-rate increases 6.56 beats for each degree of rise in temperature, and the temperature is elevated 0.127 degree for every ten beats of pulse. These figures are similar to those obtained from non-febrile subjects in this series (Table II). In this group an average of 48 points has been taken from a limited number of individuals, whereas Miss Whiting's data represent one or at most two readings from a large number of persons. The correlation coefficients run from 0.534 to -0.021 (zero), but the average of the six cases, 0.263, closely approximates Miss Whiting's value of 0.288.

In neither series is the range of temperature covered by the observations sufficient to demonstrate the true influence of temperature on pulse-rate, and therefore the figures obtained from normals or non-febrile cases are of little value, and are indeed misleading. The much wider variations of temperature observed in the febrile cases, as much as 8 or 9 degrees in some instances, accentuate this point clearly. The two exophthalmic patients were chosen as being likely to show no correlation on account of the extremely labile character of the pulse in this disease, while the other four subjects were assumed to be 'normal' as regards heat regulation and pulse-rate.

Temperature and Pulse-rate in Febrile Cases.

Of the 59 cases examined in the present series no less than 30 show correlation constants of 0.800 and upwards, indicating a very high degree of relation-

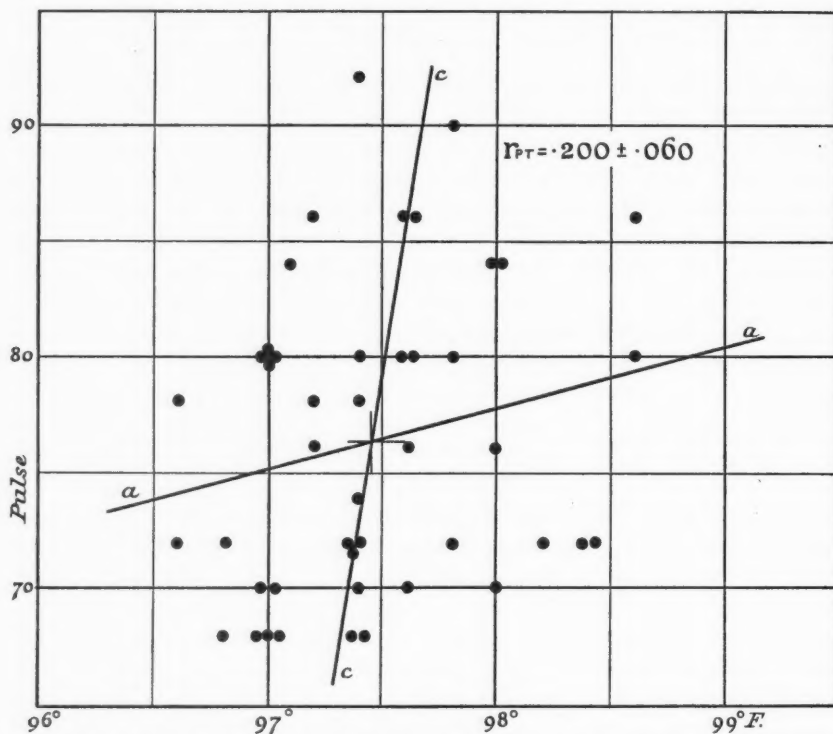


FIG. 5. (Note the different scale on this graph.) Values of pulse against temperature in a normal subject, showing the very low degree of correlation present when observations over a very limited range of temperature are available.

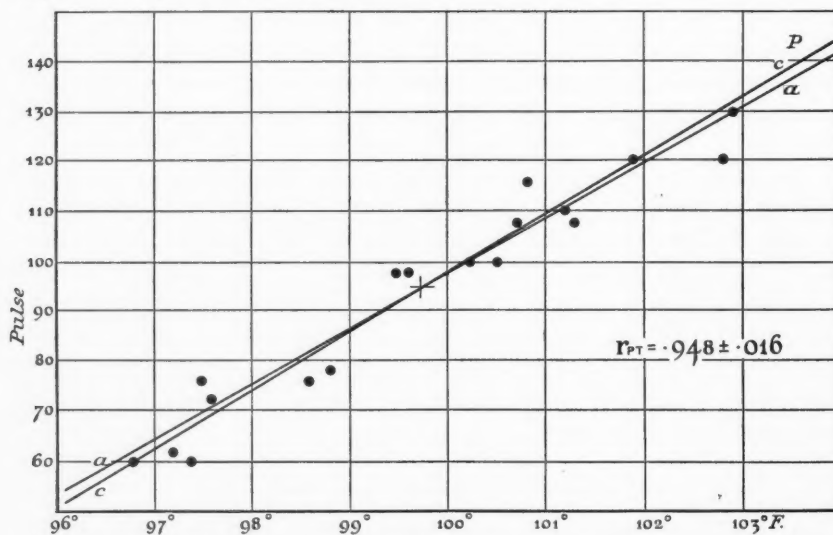


FIG. 6. Shows a higher degree of relationship between pulse-rate and temperature. The figures were observed during the reactions to three injections of peptone.

ship between pulse-rate and temperature. A further 14 (44 in all) have values over 0.600. The cases of lobar pneumonia undoubtedly show the best correlation (average of non-fatal cases, 0.891), though several of the other febrile conditions stand high in the list. Where the relationship is less perfect, disturbing factors have been looked for. It will be seen from the tables that where the patient has been receiving digitalis, salicylates, or adrenalin, the agreement of pulse and temperature is not so good. The disturbance caused by frequent ice-packs probably accounts for the low correlation in the rheumatic subject No. 37. In Case I the digitalis exhibited may explain the rather large value of the constant α —the pulse-rate under the drug declining rather more rapidly than the temperature. The findings in the series of patients who received 'protein shocks' are closely similar to those obtained in naturally occurring febrile conditions. All the correlations are of important significance (0.662 and upwards) and only four out of twenty-five fall below 0.800. As might be expected, the asthma cases stand lowest in the list. Patients 58 and 59 were receiving several injections of adrenalin daily during the periods of observation. When the tables are examined it will be noticed that—apart from certain individual variations—the constants c and α are largest when the correlations are highest, and become smaller as the correlations become less significant. These smaller constants, although giving the 'best values' warranted by the data available, probably give a poor idea of the real effect of temperature on pulse-rate, the 'other factors' obscuring this relationship. Much less variation occurs in column ' m '.

TABLE IV.

Group.	Type of Case.	Range of r .	Average r .	c .	c^1 .	α .	m .
A and E	Febrile and septic cases	0.800 and upwards	0.904	0.0967	11.04	9.13	10.02
A	Febrile cases only	" " "	0.894	0.0995	10.71	8.56	9.55
E	Peptone cases only	" " "	0.914	0.0937	11.39	9.73	10.51
E and F	All peptone cases	0.662 upwards	0.882	0.0892	12.09	9.46	10.62
A and B	Febrile cases	0.624 upwards	0.831	0.0928	11.82	8.11	9.79
B	Febrile cases	0.624–0.800	0.714	0.0806	13.87	7.28	10.22
C	Febrile cases	0.169–0.619	0.429	0.0553	23.79	4.21	9.33
A+B+C	All febrile cases	0.169 upwards	0.726	—	—	—	9.67
A, B, C, E, and F	All febrile and peptone cases	—	0.781	—	—	—	10.004

Table IV gives the averages obtained for the various constants in the different groups of cases. The figures from the natural fevers and from the 'peptone' cases are equally good and show no essential difference. The average constants in both these groups are similar and might be taken together. The values thus obtained for 43 records with correlations of 0.800 and upwards should offer the nearest approach to the true relationship of pulse to temperature.

It will be seen that the pulse-rate is advanced 9.13 beats for every 1° F. increase in temperature, and that for each additional ten beats increase in pulse-rate the temperature rises 0.967° F., equivalent to 11.04 beats per 1° F. The optimum value recorded in column 'm' is almost exactly ten beats for each degree Fahrenheit. The figures from all groups having coefficients of 0.600 and upwards are fairly similar, and it is only in Class C (r_{TP} less than 0.600) that any wide divergence is obvious. Even this is not apparent in column 'm', where a high degree of uniformity is present throughout all the groups and combinations.

The evidence offered seems to indicate that each rise or fall of temperature ought to be followed by a definite and parallel change in pulse-rate. Different persons vary greatly in the ratio of their pulse-rate to temperature, values as high as 15 and as low as 5 being found amongst the highest correlations (Groups A and E). Individuals repeatedly examined may also show considerable variation, as in Case 48, although remarkable uniformity may be present, as in Case 47. In addition, a certain amount of 'scatter' will be caused by other influences which may affect the rate of the heart. Thus it is not possible to predict with certainty what value of pulse-rate should accompany a given temperature. A general agreement should be evident on the temperature chart after the figures for two or three days have been recorded, and any gross departure from this should stimulate inquiry, as was pointed out by Mackenzie (4). Lack of correspondence between pulse and temperature has been found to occur chiefly at two points. When a fever patient is admitted to hospital the first few temperature readings are often unduly low, while the pulse stands high in proportion. Again, in pneumonia one of the first evidences that the case is 'going wrong' is a creeping up of pulse-rate unwarranted by the height of the temperature, which indeed may be falling. This independent movement explains the very low correlations found in the fatal cases of lobar pneumonia. The appearance of cardiac irregularities will also account for a certain amount of discrepancy.

Besides cardiac acceleration, fever produces other effects on the circulation, such as dilatation of the superficial vessels, congestion in certain local areas, and possibly alteration in peripheral resistance. On the heart itself heat and cold may alter the form of the electro-cardiogram (15), and vagal activity is diminished by heat (16), but a high temperature induces an irregular rhythm with intermissions (11). Considering these, it is rather remarkable to find that the activity of the pacemaker still bears a relation to the temperature. In this connexion it is interesting to note that several physiologists (17, 18) have observed the output of the perfused heart to be practically constant over a wide range of pulse-rates due to altered temperature. Knowlton and Starling (11) found this true for the range 33–40° C. and state that a diminution of output per minute was one of the earliest signs that the rise of temperature was exceeding physiological limits.

Liebermeister (2) suggested that three views might be taken of the relationship of pulse and temperature: (a) that the pulse-rate determined the temperature, (b) that the body heat influenced the heart-rate, and (c) that both might be affected more or less proportionately by the same stimulus. The first proposition hardly

requires discussion, while the second has been amply proved. Actual experiment has demonstrated that the cardiac pacemaker is extremely sensitive to alterations in temperature (11), and the importance of this mechanism is undisputed. Definite information is still required on the third point. Newburgh and Porter (13) investigated the question by perfusion experiments in dogs and made some interesting observations. They came to the conclusion that in pneumonia the heart-muscle was essentially normal, while pneumonic blood was distinctly poisonous to either healthy or pneumonic heart-muscle. When suddenly fed into the circulation the toxic blood led to lowering of the cardiac efficiency and lessened the duration and the area of contraction. Withdrawal of the poison restored the character of the contractions. On the other hand, in pneumonia the heart, being gradually exposed to the action of the toxin, largely adjusted itself to its poisoned food. Unfortunately their investigations yield no information regarding the effect of pneumonic products on the activity of the pacemaker. In spite of such evidence as to the recoverability of the heart-muscle and the absence of serious damage, and in spite of the present tendency of clinicians to minimize the cardiac involvement in this disease (14, 19), there can be no doubt that in the average case of pneumonia the heart is being continuously subjected to a poison which may eventually cause severe disturbance.

The high correlations found to exist between body temperature and the rate of the cardiac rhythm might be taken as support of the views of Newburgh and Porter, although they by no means veto the possibility of a direct action on the heart. On the other hand, the uniformly poor agreement in fatal cases would rather point to a separate toxic effect. The question is one of fundamental importance, but there is not sufficient evidence to justify a bad prognosis when the pulse and temperature fail to correspond, and a favourable one when the agreement is close. Further investigations on these lines might prove fruitful.

Summary.

The relationship between pulse and temperature has been examined in examples of eleven types of fever and in patients receiving intravenous peptone.

In 44 out of 59 a high degree of correlation was found to exist.

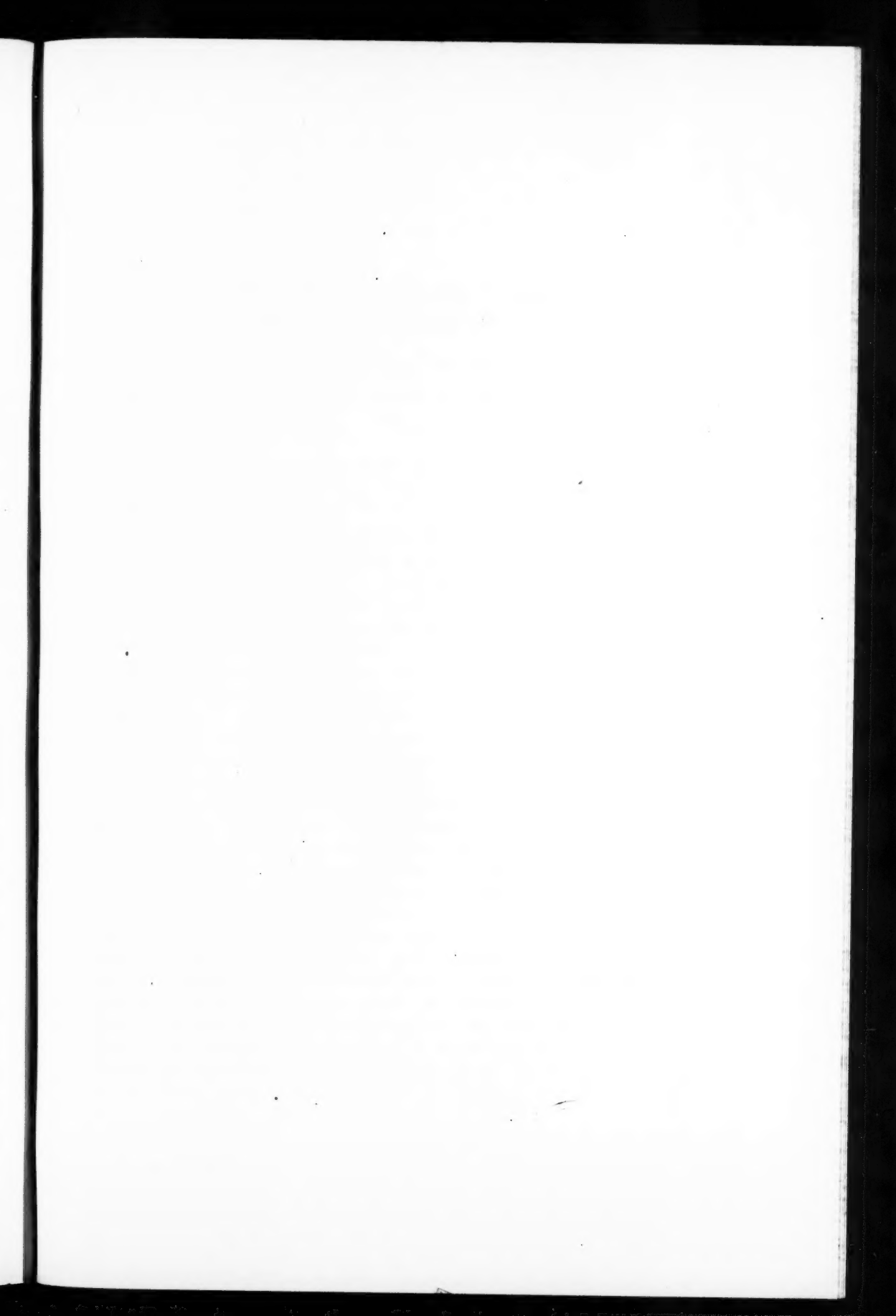
Low correlations occur in fatal cases of pneumonia.

From those cases showing the best agreement between pulse-rate and temperature, it is found that each increase of 1° F. causes a rise in pulse-rate of 9.13 beats, and that an increase of 10 beats in the pulse-rate is accompanied by 0.967° F. rise in temperature. In round figures a rise or fall of 1° F. corresponds to a change of 10 beats in the pulse.

It is suggested that this pulse-rate increase in fever is in large part a passive result of the elevated temperature.

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AN ATTEMPT AT THE CLINICAL CLASSIFICATION OF PREMATURE VENTRICULAR BEATS¹

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CONSIDERATION of the causes of premature beats arising in the human ventricle has been neglected to some extent by physiologists and very greatly by clinicians.

Physiology has traced the mechanism of propagation of the impulse through ventricular muscle so that it is known whether any particular example arises in the left or right ventricular tissues. It has also been shown to be probable that the site of origin is in or adjacent to the specialized subendocardial Purkinje tissue. Furthermore, many known types of impulse, if applied to the ventricle experimentally, will provoke ventricular premature beats. These stimuli may be mechanical, as touch or a prick; thermal; circulatory, as tying a coronary branch; chemical, as the local application of the crystals of certain salts; pharmacological; electrical; and nervous.

Thus the site of origin and the direction of propagation of premature beats, together with many experimental causes, are known. Two further theories in reference to their mechanical production, that of re-entry and that of parasystole, have sufficient confirmatory evidence to make it probable that each is responsible for some cases; indeed between them they may be responsible for all cases.

Work hitherto done has been largely directed to an investigation of the premature beat when it has arisen; there has been very little attempt to correlate the underlying pathological cause and the type of premature beat evoked.

The conclusions reached by clinicians upon this subject are on the whole unsatisfactory. One school of thought insists that the presence of premature beats indicates some local myocardial change, and that no heart exhibiting them can be considered as being completely normal. Another suggestion is that their presence is to be completely disregarded. Mackenzie's view is still, probably, the one that finds the most general acceptance. He stated that in the careful examination of young and old it is surprising to find how frequently extrasystoles are detected in healthy and robust subjects. He continued that they are rare before the age of 20, very frequent between the ages of 40 and 50, and to be expected in all people over the age of 60.

¹ Received September 11, 1926.

With regard to prognosis, he stated that in themselves they were not signs of any specific injury to the heart, that a prognosis of any gravity should not be based upon their appearance alone, that they were of no significance as regards efficiency of the heart, and that the prognosis depended for better or for worse upon other signs and symptoms of failure.

The essential point that emerges from this accepted view is that when present they appear to have no relation with the degree, if any, of heart failure. This is by no means equivalent to saying that in type they have no relation to some definite cardiac lesion.

It was with the idea of determining the relation, if any, between the behaviour of premature beats under certain conditions on the one hand, with certain definite pathological conditions upon the other, that this work has been undertaken.

Method.

An attempt has been made to count accurately the actual number of normal beats and the number of premature beats occurring over fairly long periods of time.

By obtaining control curves with the patient recumbent it has been possible to contrast with these the effect of posture, exercise, atropin, and amyl nitrite, upon the number of premature beats evoked.

The recording instrument has been the string-galvanometer. By using Cohn's electrodes and all three leads two essentials have been obtained :

- I. The ready mobility of the patient.
- II. The choice of a lead in which the shape of the deflexion caused by the premature beat is quite different from that of the normal ventricular complexes.

A stop-watch is suspended beside the moving string, and after a little practice it is possible to enumerate the number of normal and of premature beats occurring during any convenient period of time. The convenient length of such period varies with the heart-rate from five to thirty seconds. Furthermore, if the number of premature beats is considerable the shorter period will prove easier to the counter.

The numbers are written down in pencil upon a sheet of paper ; feel alone is enough to ensure a clear legible score. In this way the eyes can be kept continuously upon the stop-watch and the moving string for long periods.

The fact that, in the case of premature beats arising in the ventricle, the underlying regularity of the dominant rhythm is never broken makes the counting easy. The missed ventricular response anticipated by the premature beat is counted, for the auricle in such cases is contracting, and regularity of counting is maintained. The figures written down in pencil are, for example, 15, 16/1, 16, 15/2, 16, 16, 14/1, 15. This series of figures indicates the heart-rates for successive periods of a quarter of a minute. In the second, fourth, and seventh quarters respectively, occurred one, two, and one ventricular beat. Such figures are

charted afterwards in the most convenient manner, it being possible to chart five-second periods individually, or if necessary to add them up to quarter- or half-minute periods. The method of charting used makes possible the accurate recording of the actual numbers of premature beats rather than an indication of their average rate of appearance.

Auricular premature beats have not been considered, for, owing to the fact that they are followed by ventricular complexes identical in shape with the normal, the only ocular guide as to their occurrence is the unsound one of irregularity. The ventricular premature beat complexes will always in one of the three leads yield deflexions instantaneously distinguishable from the normal. This scoring method has been chosen in place of that in which a continuous photographic record is taken, because the latter necessitates the use of many yards of film for an experiment of, for example, half an hour. Specimen tracings taken at regular intervals would not yield such an accurate picture as is obtained by regular counting.

A further manner in which this work is limited is that only cases who manifest constantly a greater or a smaller number of premature beats have been examined. It is essential that there should be enough to count in order to contrast with any degree of accuracy their behaviour before and after exercise or any other experimental measure. The conclusions reached have therefore no direct bearing upon the sporadically occurring examples.

Cases. Twenty-eight cases in all are here recorded.

The cases chosen have been selected as having fairly frequent premature beats. A full history and physical examination have been in each case completed with the idea of determining—

- I. The presence of any cardiac disease.
- II. The presence of any symptoms or signs of heart failure.

The following scheme has been followed in the examination :

Name, Sex, Age.

History, with particular regard to rheumatic fever, rheumatic pains, chorea, frequent sore throats, scarlet fever, syphilis ; dyspnoea, cough, undue tiredness, palpitation ; pain and its relation to exercise ; swelling of feet and legs.

A full clinical examination has been performed. The size of the heart has been determined by palpation of the apex beat on the left, and by percussion of the right side.

The character of the cardiac impulse has been recorded. The quality of the heart-sounds and the presence of cardiac murmurs have been described.

Attention has been directed to the condition of the peripheral arteries (radial, brachial, and temporal), and the systolic and diastolic blood-pressure has been measured, both standing and sitting or lying.

Answers have been sought to the following questions :

1. Is there evidence of heart disease ?
2. Is there heart failure ?

3. What is the relation between heart disease or heart failure to the behaviour of ventricular premature beats to

- (a) Exercise,
- (b) Amyl nitrite,
- (c) Atropin?

The following is a summary of the clinical condition of each individual case.

Case 1. Male, aged 46.

History. No rheumatic fever; no chorea; no sore throats; no scarlet fever. Malaria seven years previously, for which he was invalided from the army. Enteric twenty-five years previously; no disability after. Since the malaria he had been somewhat short of breath on exertion. His present work, which he was capable of performing, was light work in a book warehouse. Twelve months ago he became more dyspnoeic and suffered from praecordial pain after exertion. He had been treated as for dyspepsia, and was now less dyspnoeic and had no pain. He had suffered from palpitation at night after getting to bed.

On examination. A rather under-developed man. Complexion sallow. A few carious teeth. Neck and lungs normal.

Heart. Apex beat four inches from mid-line to the left in the fifth space. The impulse was normal in intensity and area. The first sound was slightly accentuated. There was a short systolic murmur at the apex not conducted to the axilla or upwards. The brachial radial and temporal arteries were slightly tortuous and slightly thickened. The blood-pressure was: 145/75 sitting, 130/70 standing.

No other abnormality discovered. Electro-cardiograph tracing showed ventricular premature beats.

Conclusion. A normal heart. No signs of cardiac failure. Signs of early peripheral arteriosclerosis.

Case 2. Male, aged 70. Appearance was that of 65.

History. No rheumatic fever; no chorea; sore throats not infrequently. Scarlet fever at 19 years of age. 'Influenza' several times. Two years ago he had had appendicitis and peritonitis, but had made a good recovery. Ten weeks ago he had had a bad 'cold', since when he had been unduly nervous and suffered from giddy attacks in the morning; headache was present in the morning, and upon standing up he could not see clearly for some moments. Dyspnoea was present after climbing stairs, especially for the last two years and a half. Cough had been present for the last ten years. He got easily tired since the severe 'cold'. There were no subjective symptoms of palpitation.

On examination. A rather spare elderly man. Head and neck natural. The thorax was of the slender long type.

Lungs natural.

Heart. Apex beat $3\frac{1}{2}$ in. from the mid-line in the fifth space. Not enlarged to the right. No epigastric pulsation. There was an apical systolic murmur conducted two inches towards the axilla. The superficial arteries appeared normal to touch and inspection. The blood-pressure sitting was 160/80. Electro-cardiograph tracing showed ventricular premature beats (inspection). No other abnormality discovered.

Conclusion. Early arteriosclerosis. No evidence of cardiac failure.

Case 3. Male, aged 60.

History. Thirty-nine years ago had had rheumatic fever. Scarlet fever as a child. No sore throats. No chorea. Seven years ago retired from the General Post Office for angina pectoris. For the last six months he had had sudden nocturnal attacks of cardiac asthma. Shortness of breath had been severe on

walking a short distance. The feet had been swollen periodically for the past few months.

On examination. A pale man, mucosae slightly cyanosed. Face and thorax thinly covered. Oedema of the legs and feet extended up to the knees.

Chest. The apex beat was $5\frac{1}{4}$ in. from the mid-line to the left in the fifth space. The cardiac impulse was diffuse, forcible, and rather short. The first sound was not clear, and a systolic mitral murmur was present at the apex. The radial arteries were somewhat thickened. The systolic blood-pressure varied from day to day from 160 to 190, and the diastolic remained about 90 mm. of mercury. Pulsus alternans was proved. The electro-cardiograph tracing showed evidence of a right bundle branch lesion and ventricular premature beats. The post-mortem later proved the presence of severe cardiac arteriosclerosis. The Wassermann reaction was negative.

Conclusions. Severe cardiac arteriosclerosis. General arteriosclerosis. Severe cardiac failure.

Case 4. Male, aged 56, a working boiler-maker.

History. There was no history of rheumatic fever, scarlet fever, or joint pains. Tonsillitis occurred thirteen years ago and twenty-five years ago, in each case lasting for about fourteen days. He had had a winter cough for some years. There had been no shortness of breath, no undue tiredness, no oedema of the feet, and no praecordial pain.

On examination. He was a thick-set short-necked man, powerfully built. Head and neck natural.

Chest. Some emphysema was present. The apex beat was $4\frac{1}{4}$ in. to the left in the fifth space. The cardiac impulse was difficult to feel. The first sound was not clear. The arteries not thickened or tortuous. The blood-pressure was 140 systolic and 78 diastolic, both sitting and standing. The electro-cardiograph tracing showed many premature ventricular beats. No other abnormality was discovered. The Wassermann reaction was negative.

Conclusions. There was no evidence of cardiac failure or of disease.

Case 5. Male, aged 17.

History. There was no history of rheumatic fever or chorea. He had had scarlet fever three years ago and was away from home six weeks. Occasionally he had suffered from mild sore throats. Sometimes he had had pains in the knees and rarely pains in the wrists and ankles. He had had no dyspnoea, cough, undue tiredness, palpitation, or oedema.

He played football and recently ran a mile and a quarter for a wager.

On examination. No abnormality of the head, neck, or abdomen was discoverable. The lungs were natural. The heart had its apex beat $3\frac{1}{4}$ in. to the left in the fifth interspace. The sounds were natural, and the pulse-rate was 48. The blood-pressure was 130 systolic and 60 diastolic, both sitting and standing. The electro-cardiograph tracing showed ventricular premature beats.

Conclusions. There was no evidence of cardiac failure or disease.

Case 6. Male, aged 25.

History. There was no history of rheumatic fever, chorea, sore throats, or scarlet fever. Five years ago he had had syphilis, for which he had received two years' treatment. The Wassermann reaction became negative then and remains so now. He had had no dyspnoea, cough, undue tiredness, palpitation, pain, or oedema.

On examination. No abnormality was found elsewhere. The apex beat of the heart was four inches to the left in the fifth space. The impulse was normal. The first sound was not quite clear at the apex, and there was a systolic murmur

at the aortic and pulmonary bases, but no thrill. The blood-pressure was 135 systolic and 70 diastolic, both sitting and standing. The electro-cardiograph tracing showed the presence of many premature ventricular beats.

Conclusions. A normal heart. No evidence of failure.

Case 7. Male, aged 10.

History. There was no history of rheumatic fever, chorea, or sore throats. He had had scarlet fever three months ago, and was away six weeks. He had had measles four years ago and pertussis three years ago, and on the previous occasion was said by the doctor to have had a 'peculiar heart'.

On examination. There was no discoverable abnormality. The apex beat was not displaced, the impulse was normal and the sounds clear. The blood-pressure standing was 100 systolic and 65 diastolic, and sitting was 105 systolic and 65 diastolic. The electro-cardiograph tracing showed premature ventricular beats.

Conclusions. No evidence of cardiac disease. No evidence of cardiac failure.

Case 8. Female, aged 65.

History. No rheumatic fever, chorea, sore throats, or scarlet fever. For the last eighteen months she had had pain in the left side, worse on walking fast. This had gradually become more severe. Dyspnoea after exercise had come on six months ago and had progressively increased. There had been no oedema of the feet.

On examination. She was slightly cyanosed. The apex beat was $4\frac{1}{2}$ in. to the left of the mid-line in the fifth space; it was hardly palpable, and the visible impulse was very small. The first sound was not loud; the second sound at the apex was ringing. There was a systolic murmur at the apex conducted towards the axilla and towards the base of the heart. The brachial and radial arteries were slightly thickened. The systolic blood-pressure was 210 and the diastolic 110. Pulsus alternans was present. The electro-cardiograph tracing showed left preponderance and a fair number of ventricular premature beats.

Conclusions. Arteriosclerosis of the heart. Heart failure.

Case 9. Male, aged 43.

History. There was no history of rheumatic fever, chorea, scarlet fever, or sore throats. He was for two years in the army from 1917 and was capable of the usual exertions. He had been troubled with flatulence and constipation. Frequently he had attacks of palpitation in bed. There was no dyspnoea on exertion, no undue tiredness, no oedema of the feet.

On examination. A normal man elsewhere. The apex beat was $3\frac{1}{2}$ in. to the left in the fifth space. The cardiac impulse was normal in amount. The sounds were all natural and clear. The superficial vessels were not thickened. The blood-pressure sitting was 135 systolic and 85 diastolic, and standing was 125 systolic and 85 diastolic. The electro-cardiograph tracing showed some premature ventricular beats.

Conclusions. No evidence of cardiac disease. No evidence of heart failure.

Case 10. Female, aged 56. Very adipose (weight = 17 stone).

History. She had had rheumatic fever twenty-five years ago, being confined to bed for seventeen weeks. Since then 'rheumatic pains' had been present occasionally in her joints, and swelling of the feet had been present in varying degrees. Dyspnoea had been present for the last eighteen months only, also palpitation and a feeling of weight over the praecordium, worse after exercise.

On examination. She was a little cyanosed and definitely dyspnoeic. A few râles were present at the bases of both lungs. No oedema of the feet at the time. The apex beat was $5\frac{1}{2}$ in. to the left of the mid-line in the fifth space,

and the impulse was rather heaving in character. The heart-sounds were faint, and no murmurs were audible. The blood-pressure sitting was 180 systolic and 90 diastolic, and standing was 190 systolic and 90 diastolic. The electro-cardiograph tracing showed premature ventricular beats.

Conclusions. There was evidence of heart failure. There was evidence of arteriosclerosis. The absence of a murmur suggested arteriosclerosis as the aetiological agent of the undoubted myocarditis, but the history suggested rheumatic fever. It was impossible to ascribe the premature beats to the one or the other cause.

Case 11. Male, aged 12.

History. He had had pertussis as a small child. There was no history of rheumatic fever, chorea, scarlet fever, or sore throats. He had had 'influenza' in 1918, and one year ago had had an acute abdominal illness with pain and vomiting, for which he was confined to bed for fourteen days. Since then there had been pains in the joints, occasionally with stiffness and swelling. He had had no dyspnoea, cough, palpitation, or oedema. After the abdominal illness he was for a while easily tired.

On examination. The apex beat was $3\frac{1}{2}$ in. to the left from the mid-line. The cardiac impulse was definitely heaving. The first sound was not clear, and was louder than normal. The blood-pressure sitting was 115 systolic and 65 diastolic, and standing was 105 systolic and 65 diastolic. The electro-cardiograph tracing showed premature ventricular beats.

Conclusions. There was no evidence of heart failure. There was evidence of carditis, probably rheumatic.

Case 12. Male, aged 40.

History. He was an iron and wood worker and had no incapacity for work. There was no history of rheumatic fever, chorea, or sore throats. He had had scarlet fever twenty years ago, being away eight weeks. The Wassermann reaction was negative. He had no shortness of breath, tiredness, palpitation, or oedema. He had had a winter cough for a number of years. Mentally he was active and rather 'highly strung', but not at all neurotic.

On examination. The head and neck were normal. A few râles were present in the right upper lobe; there was no wasting or other evidence of tuberculosis. The apex beat was $3\frac{1}{2}$ in. to the left in the fifth space. The impulse was normal in strength, size, and position. The sounds were clear, and the first sound at the apex a little loud. The blood-pressure sitting was 135 systolic and 80 diastolic, and standing was 120 systolic and 82 diastolic. The electro-cardiograph tracing showed ventricular premature beats.

Conclusions. There was no evidence of cardiac failure or disease. He was a man with an easily reacting nervous system.

Case 13. Male, aged 22.

History. There was no history of chorea or scarlet fever. He had had poliomyelitis, aged 2; rheumatic fever, for which he was in bed for one month, aged 7; and for the last eighteen months fairly frequent sore throats. He got a little short of breath on exertion, but not abnormally so, being able to run up four flights of stairs. There was no palpitation, no pain, no undue tiredness, no oedema.

On examination. The apex beat was four inches to the left in the fifth space. The impulse was slightly heaving. There was a soft mitral regurgitant murmur. The pulmonary second sound was accentuated. The blood-pressure sitting was 125 systolic and 75 diastolic, and standing was 123 systolic and 75 diastolic. The electro-cardiograph tracing showed ventricular premature beats.

Conclusions. There was evidence of a past rheumatic carditis. There was no evidence of failure.

Case 14. Male, aged 65.

History. At the age of 25 he was passed as A 1 by an insurance doctor. He had had no attacks of rheumatic fever, chorea, or sore throats. He had had scarlet fever badly as a child. The Wassermann reaction was strongly positive. There was some dyspnoea, also some pain in the left side of the chest on exertion. He was very tired at night. There was no palpitation and no oedema of the feet or legs.

On examination. The apex beat was five inches to the left in the sixth space. There was a diastolic aortic regurgitant murmur at the aortic base and at the apex, where also was heard a systolic murmur not conducted. There was abnormal systolic pulsation in the neck; the pulse was water-hammer in type. The blood-pressure sitting was 125 systolic and 65 diastolic, and standing was 125 systolic and 65 diastolic. The electro-cardiograph tracing showed ventricular premature beats.

Conclusions. There was evidence of syphilitic disease of the aortic valves, and of aortic regurgitation. There was evidence of early heart failure.

Case 15. Female, aged 65. Married.

History. She had had rheumatic fever twenty years ago, and eight years ago had had two severe attacks of tonsillitis. She had had four or five attacks of 'influenza'. There was no history of chorea or scarlet fever. The Wassermann reaction was negative. One year ago she had had a severe attack of 'influenza'. Since then she had been easily tired, dyspnoeic on exertion, had had left-sided praecordial pain made worse by exertion. She had been troubled by palpitation. There had been no oedema of the feet.

On examination. The apex beat was five inches to the left in the fifth space. The first sound was not clear and was sometimes reduplicated. There was occasionally a short localized apical systolic murmur. The aortic second sound was not increased. There was no evidence of mitral disease. Pulsus alternans was proved present. The superficial arteries were not thickened. The systolic blood-pressure was 138 and the diastolic 80. She had an early carcinoma of the cervix. The electro-cardiograph tracing showed ventricular premature beats.

Conclusions. There was evidence of severe myocardial change, probably secondary to coronary disease. There was severe left-sided heart failure.

Case 16. Female, aged 52.

History. There was no history of rheumatic fever, chorea, or sore throats. She had had scarlet fever thirty-one years ago, being away seven weeks. She had sudden attacks of palpitation and fullness in the throat of abrupt onset and cessation. Between the attacks there was no dyspnoea, undue tiredness, pain, palpitation, or oedema of the feet.

On examination. The apex beat was $3\frac{1}{2}$ in. to the left in the fifth space. The impulse was thrusting. The first sound was not clear. On lying down a systolic apical murmur was present, conducted two inches towards the axilla. The blood-pressure sitting was 135 systolic and 85 diastolic, and standing was 125 systolic and 90 diastolic. The electro-cardiograph tracing showed ventricular premature beats.

Conclusions. There was evidence of carditis, probably rheumatic. There was no evidence of heart failure.

Case 17. Female, aged 16.

History. There was no previous history of rheumatic fever, chorea, or scarlet fever. For two years she had had sore throats and occasionally 'growing pains'. Eight weeks ago she had had a severe sore throat, fever, and pains in the shoulders and over the praecordium. She was admitted to St. Bartholomew's

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Hospital with an attack of rheumatic fever. There was now some shortness of breath on exertion, considerable palpitation, and limitation in the response to exercise. There was no oedema of the feet.

On examination (at the time of investigation). The apex beat was five inches to the left in the fifth space. The cardiac impulse was heaving and diffuse. There was a blowing systolic murmur at the apex conducted into the axilla. The blood-pressure lying was 125 systolic and 80 diastolic. The electro-cardiograph tracing showed premature ventricular beats.

Conclusions. Recent active rheumatic carditis. Evidence of early heart failure.

Case 18. Female, aged 38.

History. There was no history of sore throats, rheumatic fever, or chorea. She had had scarlet fever in childhood. For the last ten years there had been several mild attacks of haemoptysis, usually after exercise. Dyspnoea was present, especially after walking up hills. She had no cough and had had no oedema. Palpitation was present after exercise.

On examination. The apex beat was in the fifth space, four inches to the left. There was a short presystolic thrill at the apex. The first sound was short and loud and was followed by a short presystolic murmur. The pulmonary second sound was accentuated. The blood-pressure sitting was 120 systolic and 90 diastolic, and standing was 100 systolic and 80 diastolic. The electro-cardiograph tracing showed ventricular premature beats.

Conclusions. Mitral stenosis probably rheumatic. Slight limitation of cardiac efficiency.

Case 19. Female, aged 29.

History. There was no history of rheumatic fever, chorea, or scarlet fever. For the last five years she had had frequent sore throats; for the last three years she had had occasional pain and stiffness in the joints, chiefly of the hands. Dyspnoea had been present for two years, not severe. There was no cough or oedema of the feet. Palpitation had been present for the last year.

On examination. There was a mitral complexion. The apex beat was four inches from the mid-line to the left in the fifth space. The pulse was slapping. The first sound was short and loud and was followed by a presystolic murmur localized to the apical region. The pulmonary second sound was not accentuated. The blood-pressure sitting was 130 systolic and 90 diastolic, and standing was 110 systolic and 90 diastolic. The electro-cardiograph tracing showed ventricular premature beats.

Conclusions. Rheumatic mitral stenosis. Slight limitation of cardiac efficiency.

Case 20. Female, aged 65.

History. There was no history of rheumatic fever, chorea, scarlet fever, or sore throats. For the last six weeks she had had pain in the left side, this not increased by exertion or after food. She had had palpitation after exertion for the past few weeks. There was some shortness of breath. She had to rest after two flights of stairs. There had been no oedema of the feet.

On examination. The apex beat was $3\frac{1}{2}$ inches to the left in the fifth space. The first sound was not quite clear. No murmurs or other abnormalities were present. The blood-pressure sitting was 140 systolic and 70 diastolic, and standing was 128 systolic and 70 diastolic. The radial arteries were slightly thickened. The electro-cardiograph tracing showed ventricular premature beats.

Conclusions. Early arteriosclerosis. No cardiac failure.

Case 21. Male, aged 13.

History. There was no history of rheumatism, chorea, sore throats, or scarlet fever. The heart was found to be irregular. There had been no dyspnoea, undue tiredness, or oedema of the feet.

On examination. The heart was normal in position, size, and sounds. The blood-pressure sitting was 116 systolic and 62 diastolic, and standing was 105 systolic and 62 diastolic. The electro-cardiograph tracing showed premature ventricular beats. These were not caught on the film.

Conclusions. No cardiac disease. No cardiac failure.

Case 22. Female, aged 40.

History. There was no history of rheumatic fever, chorea, sore throats, or scarlet fever. She had had malaria badly seven years ago and slighter attacks for the next two years. For the last six months she had had dyspnoea on walking upstairs, and palpitation. There was no history of cough or undue tiredness. Upon the flat she could walk ten miles.

On examination. The apex beat was four inches to the left in the fifth space. The impulse was short and slapping. There was an apical presystolic thrill. The first sound was sharp, and there were both presystolic and systolic mitral murmurs. The blood-pressure was 148 systolic and 98 diastolic. The electro-cardiograph tracing showed ventricular premature beats.

Conclusions. There was mitral stenosis and probably old rheumatic carditis. There was slight cardiac inadequacy.

Case 23. Female, aged 46.

History. Three and a half years ago she had had pains and stiffness in the shoulders after a confinement. Since then she had had three attacks of tonsillitis. For three and a half years she had had increased dyspnoea after exertion, slight cough, and palpitation at night. There had been no oedema.

On examination. The apex beat was $4\frac{1}{2}$ inches to the left in the fifth space. The cardiac impulse was increased. The first sound at the apex was accentuated, and there was a distant systolic murmur there which was conducted into the axilla. The blood-pressure sitting was 140 systolic and 80 diastolic, and standing was 140 systolic and 80 diastolic. The electro-cardiograph tracing showed ventricular premature beats.

Conclusions. Chronic rheumatic mitral disease. Slightly impaired cardiac efficiency.

Case 24. Male, aged 61.

History. There was no history of rheumatic fever, chorea, sore throats, or scarlet fever. For the last three years he had had some praecordial soreness, worse on exertion, also some dyspnoea. There had been no palpitation, cough, or undue tiredness.

On examination. The apex beat was $4\frac{1}{2}$ inches to the left in the fifth space, and was normal in area and force. The sounds were natural. The blood-pressure sitting was 200 systolic and 100 diastolic, and standing was 180 systolic and 98 diastolic. The electro-cardiograph tracing showed ventricular premature beats.

Conclusions. Arteriosclerosis. No evidence of heart failure.

Case 25. Male, aged 55.

History. There was no history of rheumatic fever, chorea, scarlet fever, sore throats. The Wassermann reaction was negative. For the last two months he had felt weak. For six weeks dyspnoea and palpitation had been marked after exertion, and he had also felt dizzy on standing up. For the last three weeks he had had nocturnal attacks of dyspnoea. There had been no oedema of the feet.

On examination. Cheyne-Stokes breathing was present during sleep. The apex beat was in the fifth space, four inches from the mid-line. The cardiac impulse was forcible and diffuse. There was an aortic regurgitant murmur at base and apex. The radial, brachial, and temporal arteries were thickened and tortuous. The systolic blood-pressure lying was 150 and the diastolic 70. The electro-cardiograph tracing showed ventricular premature beats.

Conclusions. There was severe arteriosclerosis. There was some aortic regurgitation and some degree of heart failure.

Case 26. Male, aged 79.

History. There was no history of rheumatic fever, chorea, sore throats. He had had scarlet fever as a child. The Wassermann reaction was negative. For the last year he had had dyspnoea on exertion, a little cough, and some oedema of the feet at night, but could still walk three miles each Sunday. There was also, after hurrying, a little praecordial pain.

On examination. The apex beat was $4\frac{1}{2}$ inches to the left in the fifth space. The impulse was not diffuse or unduly forcible. Some epigastric pulsation was visible. The sounds were natural except for a little roughening of the first at the apex. The systolic blood-pressure was 200 and the diastolic was 90. The electro-cardiograph tracing showed ventricular premature beats.

Conclusions. Arteriosclerosis. No heart failure.

Case 27. Male, aged 48.

History. There was no history of rheumatic fever, chorea, sore throats, or scarlet fever. The Wassermann reaction was strongly positive. For the last two years he had had dyspnoea and praecordial pain, both worse on exertion. He had had a cough for seven years, and slight haemoptysis for the last six months. There were no signs of aneurysm of the aorta or of phthisis.

On examination. The apex beat was four inches to the left in the fifth space. The cardiac impulse was firm but not heaving. The first and second sounds were both loud at the apex, and the aortic second sound was not clear. The blood-pressure was 170 systolic and 128 diastolic. The urine contained a trace of albumin. The electro-cardiograph tracing showed premature ventricular beats.

Conclusions. There was evidence of arteriosclerosis, possibly of syphilitic origin. There was evidence of early cardiac failure.

Case 28. Female, aged 40.

History. There was no history of rheumatic fever, chorea, scarlet fever, or sore throats. She had for four years suffered from pain in the head, neck, and praecordium, and from attacks of palpitation. There had been no dyspnoea, cough, undue tiredness, or swelling of the feet.

On examination. The apex beat was $4\frac{1}{2}$ inches to the left in the fifth space. The cardiac impulse was slightly accentuated. The first sound was loud standing and was not clear lying. There was no definite murmur. The pulmonary second sound was accentuated. The lungs were normal. The abdomen was normal. The peripheral arteries were not thickened or tortuous. The blood-pressure standing was 115 systolic and 84 diastolic, and sitting was 135 systolic and 84 diastolic.

Conclusions. There was evidence of some degree of hypertrophy and dilatation of the left ventricle. There was no evidence of arterial disease.

These 28 cases can be divided under the following heads:

- I. Normal cases (4, 5, 6, 7, 9, 12, 21).
- II. Rheumatic cases not showing failure (11, 13, 16).

- III. Rheumatic cases showing failure (17, 18, 19, 22, 23).
- IV. Syphilitic case (14).
- V. Arteriosclerotic cases not showing failure (1, 2, 20, 24, 26).
- VI. Arteriosclerotic cases showing failure (3, 8, 10, 15, 25, 27).

The generally accepted statement that premature ventricular beats have no clear relationship with any clinical condition or with the presence of heart failure will make it probable that the cases with failure and those without will react in a similar manner, as regards premature beat frequency, to exercise or any other stimulus. The division is made here to show that this expected result is indeed true. It is noteworthy that in the 'normal' cases there is a history in three of scarlet fever, in one of joint pains, and in one of syphilis, from a total of eight.

Reaction of Premature Beats to Exercise.

Three curves are shown to demonstrate the effect of exercise upon the frequency of premature beats. The first is taken from Case 5, the second from Case 26, and the third from Case 8 (Figs. 1, 2, and 3. See also Figs. 4, 5, 10 11). Each curve of heart-rate shows four divisions:

1. The resting period.
2. The acceleration phase.
3. The deceleration phase.
4. The post-deceleration period.

The resting period is always protracted to a length that will be adequate for an estimation of the number of premature beats occurring during rest. During the acceleration phase the heart-rate cannot be counted, for the movements of the skeletal muscles cause deflexions that render enumeration impossible, even should the string itself escape injury. The exercise in all cases consisted in stepping up upon a chair eighteen inches high, and down again upon the floor, a sufficient number of times to cause dyspnoea. The amount of exercise varied greatly and unavoidably from patient to patient. In cases of severe cardiac incapacity this form of exercise was replaced by that of raising the thorax to the upright from the recumbent position a stated number of times.

During the deceleration phase the number of normal and of ectopic beats is easily countable simultaneously.

The important period from the point of view of the results obtained during this investigation appears to be the post-deceleration period, when the heart has recovered from the exercise tachycardia to a level in most cases equal to that which obtained before exercise.

The effect of exercise upon the number of premature beats during this period is given in the following table.

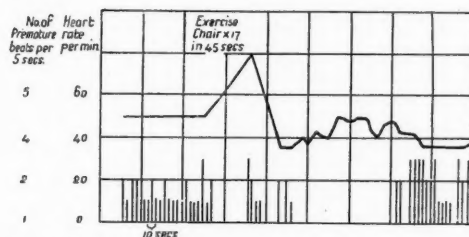


FIG. 1. The effect of exercise upon premature beat frequency after deceleration. (Normal or Rheumatic Groups.) There is an actual decrease in the number.

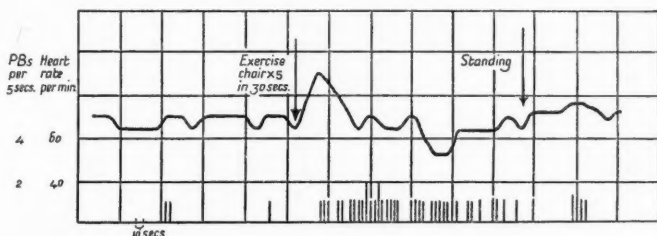


FIG. 2. The effect of exercise upon the number of premature beats in the post-deceleration period in arteriosclerosis. There is an actual increase in the number.

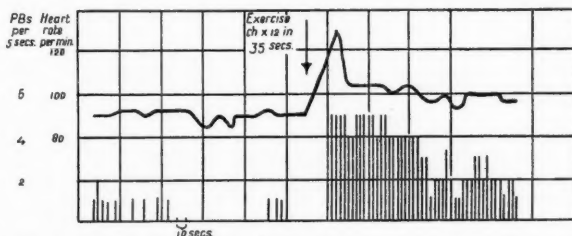


FIG. 3. The effect of exercise upon the number of premature beats in the post-deceleration period in arteriosclerosis. There is an actual increase in the number, the rate being slightly raised.

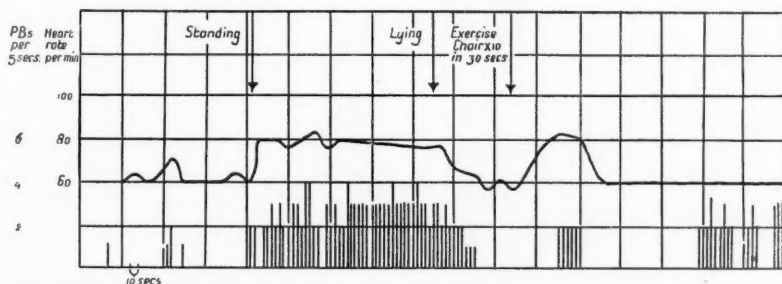


FIG. 4. The effect of standing upon premature beat frequency. Note the correspondence between pulse-rate and premature beat frequency. Standing increases the number occurring and lying decreases it. There is close correspondence between pulse-rate and premature beat frequency. (See the remarks upon Re-entry.)

Case No.	Rest- ing Rate.	Exercise.*	Degree of Tachy- cardia.	Length of Decelera- tion Period.	1st Exercise.			2nd Time.			3rd Time.			Effect upon Prema- ture Beats.
					Period.	No. of P. Beats.		Period.	No. of P. Beats.		Period.	No. of P. Beats.		
						Before.	After.		Before.	After.		Before.	After.	
Normal Cases.														
4	84	secs.	120	secs.	secs.	62	39	—	22	0	—	201	172	—
5	48	10 in 30	84	35	110	31	3	125	22	0	110	—	—	—
6	68	17 in 45	88	60	100	56	44	150	0	0	—	150	—	0
7	104	20 in 45	128	45	100	30	25	125	24	18	125	14	15	—
9	64	10 in 35	96	80	150	30	3	—	—	—	—	—	—	—
12 ^a	74	14 in 35	98	45	150	2	40	125	11	33	125	5	0	—
12 ^b	76	14 in 35	120	60	—	—	—	—	—	—	—	—	—	—
21	80	20 in 60	112	60	150	1	2	—	—	—	—	—	—	0
912 156 Unclassified.														
28	72	10 in 40	120	secs.	secs.	0	0	(Present on standing up only)			—	—	—	0
Rheumatism (no failure).														
11	80	secs.	144	secs.	secs.	1	0	150	7	6	—	—	—	0
13	76	15 in 35	120	35	150	50	40	150	46	41	150	103	110	0
16	84	16 in 50	132	25	150	13	11	150	2	6	—	—	—	—
		15 in 30		70										
84 51 Rheumatism (failure).														
17	106	secs.	106	secs.	secs.	56	64	100	38	35	—	—	—	0
18	88	5 in 12	132	60	300	30	28	100	27	26	—	—	—	0
19	100	14 in 30	144	50	100	30	12	150	41	37	—	—	—	—
22	88	10 in 30	112	15	60	22	17	—	—	—	—	—	—	—
23	60	10 in 30	108	90	150	2	0	—	—	—	—	—	—	—
23	60	14 in 45		50	150	0	0	150	0	0	—	—	—	0

* i.e. number of times of stepping on to a chair in so many seconds.

110 121

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		<i>Syphilis (failure).</i>											
		secs.	secs.	secs.	secs.	secs.	secs.	secs.	secs.	secs.	secs.		
14a	60	96	15 in 50	—	—	—	—	—	—	—	—	—	+
14b	63	84	8 in 40	—	—	—	—	—	—	—	—	—	+
<i>Arteriosclerosis (no failure).</i>													
1	60	96	10 in 30	secs.	secs.	secs.	secs.	secs.	secs.	secs.	secs.	secs.	+
2	54	72	9 in 15	120	55	0	3	—	—	—	—	—	+
20	76	144	10 in 25	10	100	8	11	—	—	—	—	—	+
24	80	120	5 in 15	75	100	3	9	—	—	—	—	—	+
26	68	92	5 in 30	40	60	1	5	—	—	—	—	—	+
				45	150	3	25	—	—	—	—	—	+
<i>Arteriosclerosis (failure).</i>													
3	80	120	10 in sitting up from lying position	secs.	secs.	secs.	secs.	secs.	secs.	secs.	secs.	secs.	+
				45	100	4	8	—	—	—	—	—	+
8	98	132	12 in 30 secs.	120	125	3	94	50	100	23	6	—	+
10	90	120	5 in 15 secs.	65	150	60	29	150	75	54	32	—	+
15	84	98	10 sitting up from lying position	15	150	47	54	—	—	—	—	—	+
25	72	92	10 sitting up from lying position	45	60	0	28	150	—	—	—	—	+
27	72	0	30 sitting up from lying position	0	300	19	23	—	—	—	—	—	+

133 936
87 145

In eight normal cases there was a decrease or no change in the number of premature beats in seven. In three rheumatic cases without failure and five with failure there was an increase in the number of premature beats after exercise in one only. There was an increase in the number after exercise in the four out of five cases of arteriosclerosis without failure and in five out of six with failure.

There would thus appear to be considerable divergence in the behaviour of the number of premature beats after the deceleration period after exercise according to whether there is evidence of arteriosclerosis or not.

It is seen that the ages of all patients, irrespective of the pathological condition found, in whom an increase, during the post-deceleration period, in the number of premature beats occurred are respectively 40, 40, 65, 70, 65, 61, 81, 46, 60, 59, 56, 65, 55, and 48 years. Of these all but the first three showed evidence of arteriosclerosis.

Of the three exceptions the first (Case 12) will be discussed later, the second (Case 22) had had malaria and was a case of mitral stenosis, the third (Case 14) was one of syphilitic aortic regurgitation.

The distinctive pathological lesion that separates the group of cardiac arteriosclerosis from the rheumatic group is that of disease of the larger cardiac vessels. Chronic inflammatory myocardial lesions are common to both groups, as is the presence of local fibrosis.

It is therefore suggested that the reason for the increase in the number of premature beats after the deceleration period following exercise is to be found in the production of some local myocardial anoxaemia resulting from a greater or lesser degree of disease in some branch of a coronary vessel. That such a lesion is essentially local is suggested by the fact that the presence or absence of failure, whether in the rheumatic or in the arteriosclerotic group, appears to have no influence upon the behaviour of the premature beats to exercise. Moreover, in any particular case the premature beats are generally of constant shape. It is the type, not the degree of the lesion, that seems to be the determining factor.

The Effect of Graduated Exercise.

In order to define more accurately the relation of the premature beat frequency to exercise, certain of the cases (Nos. 3, 5, 7, 8, and 20) were given increasing amounts of exercise with the idea of attempting to determine whether the increase or decrease in the number of premature beats varied at all in proportion.

Case 3, being a very ill man, could not be severely exercised. From his semi-recumbent position upon a couch he was asked to raise himself slightly leaning forward in an attempt to touch his toes. The first exercise comprised this movement performed 7, the second 14, and the third 21 times. The 40 seconds period before the first exercise contained 12 premature beats. That following contained (counting after the deceleration period) 13, that after the second 17, and that after the third 17, but the rate here was raised from 85 to 90, where it remained.

Case 5 was given the following three exercises of stepping up on to a chair 5 times, 10 times, and 20 times. The number of premature beats was unaffected by all three degrees of exercise.

Case 7 was exercised by being made to step up on to a chair 5 and 10 times. The premature beat frequency remained unaffected by either exercise.

Case 8 was exercised by being made to step up on to a chair 5, 10, and 20 times. The number of premature beats before exercise (three minutes) was 4, after the first exercise (three minutes) was 4, after the second was 7, and after the third 10.

Case 17 was given the same exercise in a semi-recumbent position as was *Case 3*. She leant forwards 10, 20, and 30 times. The rate after each exercise remained up, and the premature beat frequency varied directly with the rate. There was no chance of measuring the premature beat frequency at analogous rates after a deceleration, for this did not occur.

Case 20 was made to stand upon a chair 5 and 10 times. In each case there was a definite increase in the number of premature beats. The number of premature beats present before exercise was in four minutes 2, after the first 11, and after the second 10.

It would seem, therefore, that no corresponding variation of the premature beat frequency coincided directly or inversely with a graduation in the amount of exercise within the limits mentioned.

Upon a considerable number of occasions, however, when premature beats, increased in number after exercise, are seen to occur after, for example, every third normal beat, they can be seen to die away gradually, following progressively every third, fourth, and fifth normal complex. This regularity does not appear often to extend farther, and although their disappearance may obviously be progressive it does not retain such mathematical accuracy beyond five or, at the most, six beat intervals.

The chart of *Case 26*, figured above (Fig. 2), shows the gradual disappearance fairly well.

The Effect of Posture upon the Frequency of Premature Beats.

Case 1. During a period of recumbency (five minutes) 2 premature beats were counted; on standing up, the rate being raised about 8 beats per minute, 15 were counted.

Case 5. During a period of recumbency (three minutes) 8 premature beats were counted; upon standing up many premature beats were immediately evoked, to subside nearly as quickly upon lying down. The three-minute period after standing contained 99, and the $1\frac{1}{2}$ -minute period on lying down again contained none (Fig. 4).

Case 7. (Exp. I.) The $1\frac{1}{2}$ -minute period of recumbency before standing contained 9 premature beats; that immediately after contained 8, the latter at a pulse-rate higher by 10 beats per minute. (Exp. II.) The three-minute period before standing contained 10; that after, and with a pulse-rate higher by 10 beats per minute, contained 15 premature beats.

Case 9. The $1\frac{1}{4}$ -minute period before standing contained 5; that after contained 9 premature beats. The standing heart-rate was increased by 12-20 beats per minute.

Case 11. Before standing there were in $3\frac{1}{2}$ minutes 3 premature beats; after, in the same period, and at a heart-rate 12 beats per minute higher, there were 7.

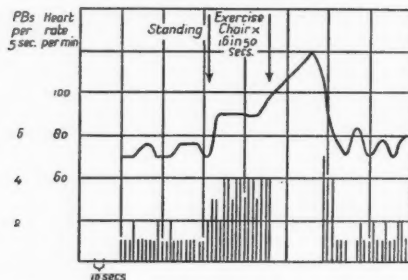


FIG. 5. The effect of posture upon premature beat frequency. Note the higher heart-rate.

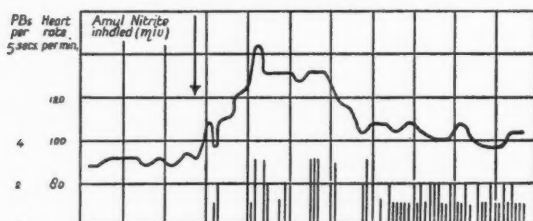


FIG. 6. The effect of the tachycardia of amyl nitrite upon the premature beat frequency in the post-deceleration phase (arteriosclerosis). There is an actual increase in the number occurring.

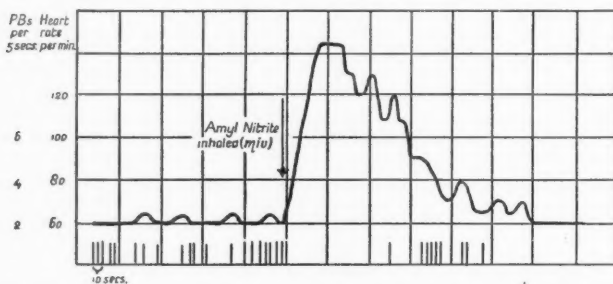


FIG. 7. The effect of amyl nitrite (normal). There is a decrease in the number of premature beats. In other normal cases there was no change.

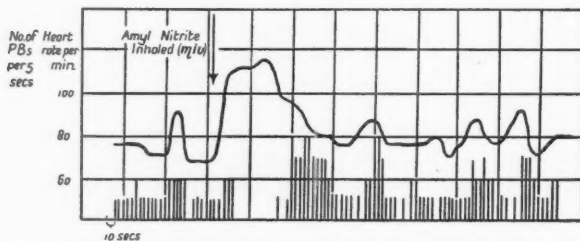


FIG. 8. The effect of amyl nitrite (normal). Note correspondence between premature beat numbers and heart-rate.

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Case 13. (Exp. I.) The period ($1\frac{1}{4}$ minutes) before standing contained 23; that after contained 55 premature beats, the heart-rate being raised by 16 beats per minute. (Exp. II.) The two-minute period before standing contained 23; that after, and at a heart-rate higher by 10 beats per minute, contained 78 premature beats (Fig. 5).

Case 28. In the recumbent position one premature beat only was seen in four minutes; upon standing up four were counted within the first half-minute, and after that no more appeared. The difference between the standing and recumbent heart-rate was 12 beats per minute.

In the following cases standing had no effect of increasing the number of premature beats:

Case.	Effect on P.B.s.	Lying Heart-rate and Blood-pressures.		Standing Heart-rate and Blood-pressures.	
2	—	52	160/70	66	160/70
6	—	68	135/70	68	135/70
12	0	72	135/80	80	120/82
14	0	78	135/65	82	135/65
20	0	76	140/70	96	138/70
21	0	84	116/62	Steady rise to 108	105/62
23	0	60	140/80	60	140/80
24	—	76	200/100	84	180/100
25	0	80		76	

— = Diminished.

0 = No effect.

In analysing the effect of posture upon the frequency of premature beats there are two main considerations. In some cases the change to the erect position produces a considerable fall in the peripheral blood-pressure. Such variation in vascular physics may conceivably produce, either directly or reflexly, an increase or otherwise in the number of premature beats. But coincidently there is frequently a raised heart-rate, and this must be taken into account. Tachycardia, other things being equal, is known to reduce the number of premature beats. Thus, if these become more frequent in spite of tachycardia, there would appear to be little doubt that the upright posture is evoking them. Again, if the pulse-rate remains constant and the blood-pressure varies, the suggestion is that this latter variation is important.

In the above table of cases in whom posture does not increase the number of ectopic beats the following seem to have an efficient vasomotor control: 2, 6, 14, 23, 25; and the following have a very considerable tachycardia coincident with the fall in systolic blood-pressure: 12, 20, 21, 24.

Consideration of the cases with an increase in the number of premature beats shows that in every case the heart-rate was considerably raised. The systolic pressure fell in Case 1, 15 mm. Hg on standing; in Case 5, 0 mm.; in Case 7, 5 mm.; in Case 9, 10 mm.; in Case 11, 10 mm.; in Case 13, 2 mm.; and in Case 28, 20 mm. On the whole, therefore, there is not a fall in peripheral systolic blood-pressure adequate to explain on this ground alone the undoubted fact that posture increased the number of premature beats. Two other factors may be found in a coincident variation in the vagus-sympathetic balance or a

simultaneous increase in the tone of both, or else some more mechanical local effect upon the heart.

The writer is inclined to believe that the variation in nervous tone may ultimately be convicted of being the more important factor.

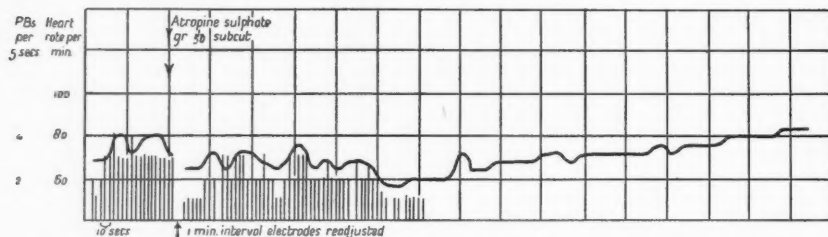


FIG. 9. The effect of atropin upon premature beat frequency. The number of premature beats falls progressively before the acceleration effect of atropin begins.

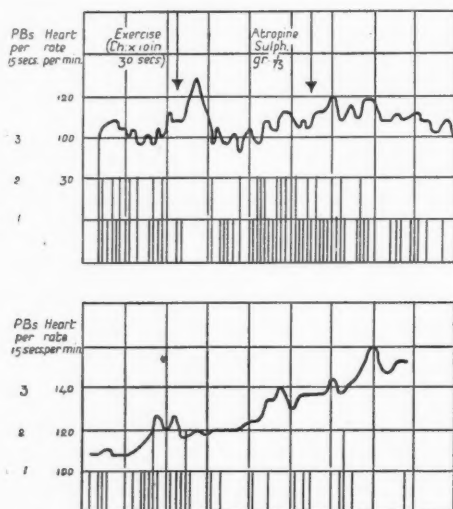


FIG. 10. The effect of atropine upon premature beat frequency.

The Effect of Amyl Nitrite.

An ampoule containing four minims was snapped and the vapour inhaled by the patient.

Amyl nitrite has a double use for the purposes of the investigations here described. It can be administered and the whole course of the acceleration, tachycardia deceleration, and post-deceleration periods can be watched, for the patient is lying motionless, and there is always a latent period sufficiently long before the effect begins. It has been the writer's practice to snap the ampoule and to get the patient to hold this at the nose with the left hand, Lead II being

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used for the enumeration of heart and premature beat rates. Should Lead III give a better curve the right hand is used. The second use of the drug is that the effect upon the number of premature beats of over-driving the heart with a diminished load can be compared to the work incurred by exercise where the load has been increased.

Taking the second of these two investigations first, the following results have been obtained :

Case No.	Number of Premature Beats.		Mean Acceleration.	Highest Rate.	
	Before Amyl Nitrite.	After Amyl Nitrite.			
1	1 in 2 min.	3 in 2 min.	5	30 beats for 4 min.	132
2	3 in 1½ "	1 in 1½ "	2	15 " " 4 "	80
3	No deceleration period.				
4	24 in 2 min.	21 in 2 min.	33	7 " " 2 "	96
5	No deceleration period counted.				
6	62 in 2 min.	47 in 2 min.	71	15 " " 1½ "	124
7	6 in 3 "	1 in 3 "	1	20 " " 1½ "	164
8	0 in 3 "	50 in 3 "	50	20 " " 3 "	144 (Fig. 6)
9	16 in 3 "	4 in 3 "	4	27 " " 3½ "	144 (Fig. 7)
10	51 in 3 "	75 in 3 "	75	10 " " 3½ "	120
11	3 in 3 "	4 in 3 "	4	25 " " 6 "	152
12	0 in 2 "	21 in 2 "	21	25 " " 4½ "	150
13	30 in 2 "	40 in 2 "	40	15 " " 2½ "	116 (Fig. 8)
14	1 in 3 "	1 in 3 "	1	12 " " 2 "	84
15	51 in 2 "	81 in 2 "	81	10 " " 2 "	110
16	2 in 2 "	6 in 2 "	6	12 " " 2½ "	120
17	47 in 2 "	31 in 2 "	31	20 " " 3½ "	156
18	39 in 2 "	19 in 2 "	19	30 " " 6 "	148
(After deceleration the rate was still higher by 18 beats.)					
19	56 in 2 min.	23 in 2 min.	35	25 beats for 2½ min.	168
22	0	0	0	20 " " 3 "	144
(15 were seen during the increased rate.)					
23	0	1	2	35 beats for 3 min.	150
(13 were counted during the increased rate.)					
24	1	0	0	10 beats for ½ min.	100

Of six cases with arteriosclerosis the number of premature beats was increased in the deceleration period after amyl nitrite in four, remained unchanged in one, and was decreased by two beats in one.

In five normal cases the number of premature beats after the deceleration period was diminished in four and increased in one (Case 12). This case is to be dealt with later.

In seven rheumatic cases the number of premature beats after the deceleration period was decreased in two, unchanged in three, and increased in two.

The effect of amyl nitrite appears to run fairly closely parallel to that of exercise. The suggestion is therefore that tachycardia is a factor of greater importance than its added load in the causation of an increase in the number of premature beats after exercise, when this occurs.

The Effect of Atropin Sulphate.

The first few cases to whom atropin sulphate was given subcutaneously did not appear to manifest any great change. It was not until Case 12 was being investigated that any indication for using it was definitely manifest.

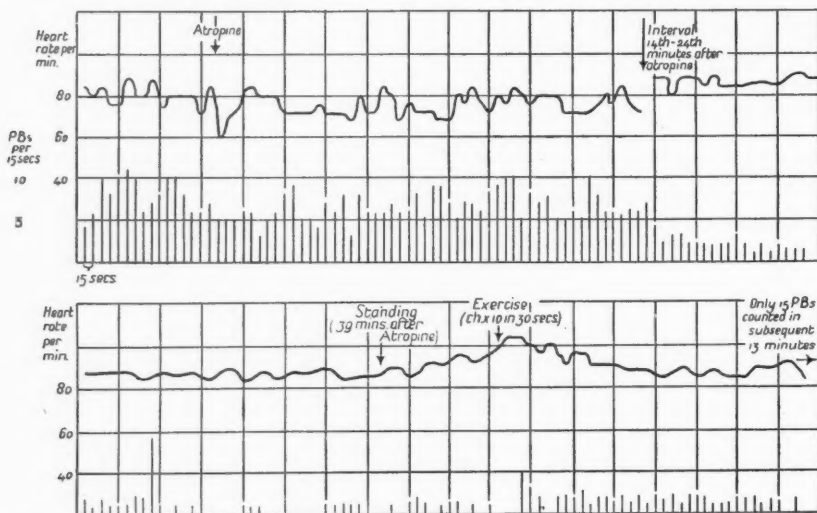


FIG. 11. The effect of atropin. On two former occasions resting, for as long a period but without atropin, was accompanied by no fall in the number of premature beats.

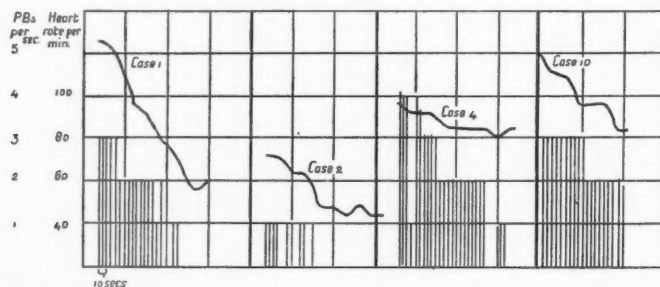


FIG. 12. The premature beat and heart-rates during deceleration after inhalation of amyl nitrite M_{iv} . When the previously raised heart-rate has fallen to a certain point premature beats appear during the deceleration period; their frequency falls synchronously with that of the heart-rate.

It was noticed in this case that the premature beats tended especially to follow longer pauses than usual between normal beats; furthermore, he was the subject of very well marked sinus arrhythmia. In the light of the work of Rothberger and Winterberg, who produced ectopic ventricular rhythms by combined vagal and sympathetic stimulation, it was considered possible that the mechanism of production of premature beats in this case was largely influenced by an excessive vagal tone.

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Atropin sulphate was therefore administered to this case and to several others with the following interesting result :

Case.	Effect upon Premature Beats during Early Slowing.	Effect upon Premature Beats during Acceleration.
2	-	-
4	-	+
5	0	0
6	-	- (Fig. 9)
7	-	- (Fig. 10)
12	-	-
13	-	+
17	-	- and + after 120
19	-	-
22	-	+
25	-	- (Fig. 11)

- = Diminished. 0 = No effect. + = Increased.

Thus in eleven cases, irrespective of aetiology, the administration of atropin sulphate, gr. 1/50, subcutaneously caused a diminution in the number of premature beats in ten. This coincided at first with the fall in rate that followed the injection, and persisted for about four minutes. When the rate rose after this preliminary slowing, the premature beats were still further decreased in seven and were increased in three. Two of these latter cases are dealt with below under the heading of 'The Theories of Parasystole and Re-entry in the Light of the Present Investigation'.

It is here suggested that the early effect of atropin is that of vagal stimulation, and that the number of premature beats occurring is diminished by the gradual and persistent change in vago-sympathetic balance that occurs, rather than by actual vagal stimulation or vagal paralysis, though it is of course conceivable that there may be an action upon ventricular muscle direct.

Whatever the explanation, there is no doubt about the fact.

The appearance of premature ventricular beats in certain patients appears to be directly due to rather abrupt changes in vagal tone as manifested by sudden slowing, like that which occurs sometimes abruptly after exercise, and by well-marked sinus arrhythmia. Such manifestations have been observed frequently during the present investigation.

The Theories of Parasystole and Re-entry in the Light of the Present Investigation.

The two theories that within recent years have been put forward to account mechanically for the production of premature beats are that of parasystole and that of re-entry.

That of parasystole postulates the presence of a centre in ventricular muscle from which impulses emanate regularly and rhythmically. The centre being shielded from interference on the part of the normal impulse by a condition of unidirectional block is able, in spite of the normal rhythm, to give rise to ventricular contraction, provided the muscle is not refractory. Such successful stimulation is only possible upon those occasions when the resting period after

a normal beat coincides with a stimulus production from the ectopic focus. When heart-rate and the length of the refractory periods are taken into account these intervals are necessarily not very frequent.

Theoretically under these circumstances any increase in the refractory period should make premature beats less frequent.

In the present series of cases are three examples showing pulsus alternans (Cases 3, 8, 15). In each case the pulsus alternans was present especially after exertion, and presumably in each case was the refractory period coincidently prolonged, and in each case the effect of exercise was to increase the number of premature beats occurring after exertion. (See Figs. 3 and 4.)

The pulsus alternans was proved by pulse-tracings in two of the cases and by blood-pressure readings in all three.

A completely regular rhythm was shown to have sets of alternate beats, having a difference in Case 3 of 15, in Case 8 of 15, and in Case 15 of 12 mm. of mercury.

With regard to the theory of re-entry one would expect to find in cases showing it a close correlation between heart-rate and premature beat frequency at rates below that where the refractory period of a preceding beat came unduly close to the following normal beat.

Certain of the cases described in the present communication seem to show this condition. During the height of the tachycardia premature beats are absent, conceivably being crowded out, but during the deceleration period they reappear in much greater numbers than before, falling with the rate until in the post-deceleration phase they are equal to or less than the numbers appearing before acceleration.

This seems to be true whatever the cause of the tachycardia. It is most easily seen in the amyl nitrite curves. In Cases 1, 2, 4, 10, 13, 15, 22, 23, and 27 the premature beats are very considerably more in number during the deceleration phase following amyl nitrite inhalation. (See Fig. 12.)

The higher standing heart-rate found in Cases 1, 7, 9, 11, and 13 is accompanied by a marked increase in the numbers of premature beats present. (See Figs. 4 and 5.) Case 13, after amyl nitrite, shows an increased heart-rate from time to time, and coincident with this an increase in the number of premature beats occurring (Fig. 8).

These two findings would appear to favour the theory of re-entry, and even to make very unlikely that of parasystole in these thirteen cases. About the remaining fifteen cases there is no strong evidence either way.

Conclusions.

I. A method is described for enumerating accurately, over long periods of time, the number of normal and of premature ventricular beats.

II. The effects of exercise, posture, amyl nitrite, and atropin upon the number of premature beats, and simultaneously upon the heart-rate, have been

studied in a series of twenty-eight cases, in whom such premature beats were of reasonably frequent occurrence.

III. Exercise would seem to diminish or to leave unchanged the number of premature beats after the deceleration period (comparing them with those occurring during an equal period preceding the exercise) in normal and in rheumatic cases. Exercise would seem to increase their number after the deceleration period in cases with evidence of arteriosclerosis or of coronary disease.

IV. Amyl nitrite appears, though in a less clear-cut manner, to have a similar effect to that of exercise.

V. Atropin, during the early slowing and during the later acceleration, diminishes the number of premature beats irrespective of their aetiology or pathology.

VI. Posture has a definite effect. Standing causes an increase in the number of premature beats.

VII. The curves taken from thirteen of these cases suggest re-entry rather than parasystole as being a causative mechanism.

The writer desires to thank the physicians of St. Bartholomew's Hospital who have generously given him the opportunity of investigating their cases, also Dr. Parsons Smith of the Heart Hospital, who kindly referred several cases to him.

OBSERVATIONS UPON THE CIRCULATION RATE IN MAN BY THE ETHYL IODIDE METHOD¹

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From the Department of Therapeutics, University of Edinburgh.

General Considerations.

THE recently published method of Henderson and Haggard (1) for estimating the general circulation rate in man by means of ethyl iodide promises such valuable results, both in the physiological laboratory and in the clinic, that it demands very serious consideration. Other previously described methods for estimating circulation rate in man, such as those of Krogh and Lindhard (2), Douglas and Haldane (3), Meakins and Davies (4), Field, Bock, Gildea, and Lathrop (5), Burwell and Robinson (6), require such extensive manipulation or such active and intelligent co-operation on the part of the subject as to make them unsuitable for routine clinical work, or for the investigation of the more severe types of cardiac disease. The ethyl iodide method, however, requires from the subject no more effort than is involved in the estimation of the basal metabolic rate, i. e. breathing through a mouthpiece for ten to fifteen minutes, and, with apparatus suitably designed and properly cared for, entails absolutely no discomfort or respiratory resistance. Indeed we have found not infrequently that during the test the subject tends to doze, or may even fall asleep. The object of the present paper—admittedly very incomplete—is to indicate various technical difficulties which we have encountered, to suggest various slight modifications in the method, and to illustrate the variability of the findings in normal individuals unless very carefully standardized conditions are maintained.

For the benefit of those readers who have been unable to consult the original paper of Henderson and Haggard, the following brief description of the principles involved in the method may be of interest. Ethyl iodide (C_2H_5I) is a substance which when inhaled is readily taken up, in accordance with the ordinary physical laws of solution, by the blood passing through the lungs. After passing into the blood it is rapidly hydrolysed in accordance with the equation



With the concentration and amount of ethyl iodide used in the method, it has been shown that little or none of the substance returns unaltered to the lungs in the venous blood. If, then, we know the amount (P) of ethyl iodide absorbed

¹ Received September 28, 1926.

The liberated iodine is collected in potassium iodide solution and its amount

estimated by titration with sodium thiosulphate solution of suitable strength, using starch paste as an indicator.

Modifications in the Apparatus.

Ethyl iodide is decomposed or absorbed in the presence of rubber, and for this reason Douglas bags cannot be employed in place of the spirometer. We found that an appreciable error in the determination of the circulation rate arose from the fact that ethyl iodide vapour reacted with the rubber of the non-collapsible corrugated tubing leading to and from the respiratory valves of the mouthpiece. As both inspiratory and expiratory tubes reacted with the vapour the amount of iodide apparently absorbed by the subject was too high, part being absorbed by the rubber and part by the patient, so that the apparent circulation rate was sometimes more than double the actual. This difficulty was surmounted by employing flexible metal tubing of similar bore. Ethyl iodide reacts with exposed metals, and it was therefore necessary to coat the insides of both tubes and of the metal mouthpiece with red lead. After passing air containing ethyl iodide through six feet of this tubing there was no change in its concentration. Since employing this modification estimations of the circulation rate have been more consistent and have been within the same range as those determined by other means. All rubber parts exposed to ethyl iodide throughout the apparatus must be reduced to a minimum. For the same reason it is necessary to replace the finer tube for the collection of alveolar air by a tube of metal flex (coated inside with red lead) of similar bore.

In our recent work we have discarded all other types of respiratory valves in favour of the old-fashioned Lovén valves (7). The valves described by Henderson and Haggard were tried by us, and it was found that on the expiratory side they soon became moist from condensation of water in the expired air. This moisture caused the somewhat large apposing surfaces of rubber to stick together and produced a disconcerting degree of resistance to expiration. Other types of valves have this same disadvantage. With the Lovén valve, however, there is only a very narrow rim of metal in contact with the diaphragm, and the condensed moisture from the expired air causes no appreciable increase in resistance. For the diaphragm, in place of the goldbeater's skin originally described, we have used rubber dam, and it is important in fitting new diaphragms to see that it is not tightly stretched. Such valves work perfectly, require little or no attention, and cause no respiratory disturbance to the patient. Many subjects fall asleep while breathing through them.

The ethyl iodide in the spirometer must be kept well mixed during the determinations. This is accomplished by a rotary fan in the spirometer. To ensure the collection of a thoroughly mixed inspiratory sample, we employ a five-litre mixing-bottle on the inspiratory as well as the expiratory side of the mouthpiece. Duplicate samples are taken by water displacement from the inspiratory and expiratory flasks during the determination.

In the analysis of the collected samples Henderson and Haggard employ an oil bath. It is essential to keep the iodine pentoxide U-tubes at a steady and uniform temperature. To accomplish this we employ an electrically heated hot-air oven with a thermostat control. Apart from the danger of an explosive reaction between boiling oil and the pentoxide, this electric oven is much more convenient, and with an efficient thermostat more compact and reliable. A stream of outdoor air may be sucked through the tubes by means of a filter pump. We have found, however, that an electric pump is more reliable and the flow of air more readily regulated.

Technique employed.

The subject having rested sufficiently, the spirometer is filled and the mouth-piece adjusted. Breathing is now commenced from the spirometer and the alveolar air bubbling in the Müller valve adjusted. Between 10 and 20 c.c. of alveolar air must be drawn over with each respiration in order to ensure the collection of a thoroughly mixed sample. This amount is the more easily estimated if the bubbles are made slightly more permanent by the addition of a trace of saponin to the water in the Müller valve. As respiration proceeds the inspiratory flask is gradually washed out with the ethyl iodide mixture from the spirometer. After about 30 litres have been breathed the concentrations of ethyl iodide in the flask and spirometer are identical, and a reading is then taken from the spirometer. The period of determination is measured from this point by employing a stop-watch. Ten to fifteen minutes will suffice. This technique ensures the collection of a reliable alveolar air sample, the dependability of which can readily be checked by CO_2 analysis. About the middle of the period simultaneous inspiratory and expiratory samples are collected in the 250 c.c. tubes from the respective flasks and again at the end of the period. An additional sample from the expiratory flask (taken into an evacuated Haldane sampling tube) is analysed for CO_2 and O_2 in order to determine the oxygen consumption per minute. Pulse-rate, respiratory-rate, and blood-pressure determinations are made at convenient intervals during the period of observation. The samples containing ethyl iodide are then exposed in the suction train to the pentoxide U-tubes. We employ a ten-minute period, during the first five minutes of which the rate of flow of air is less than a quarter of a litre per minute and for the last five much faster. Constant rates of flow are essential in order that all the iodide may react with the pentoxide (8). The iodine collected is titrated against sodium thiosulphate of constant strength, in the manner described by Henderson and Haggard.

Ethyl iodide is an unstable substance and tends to decompose if exposed to the air and light for long periods. In decomposing it turns a yellow-brown colour, due to the presence of free iodine. It is therefore stored in sealed amber-coloured ampoules, and only a little kept ready for use at a time. The decomposition upsets the determinations, and on the liquid becoming a pale yellow colour redistillation is necessary.

The technique described above is soon acquired, readily carried out, and is found to yield reasonably consistent results even in subjects unaccustomed to respiratory experiments.

Discussion of Results.

We have tabulated the findings in 118 determinations on 18 subjects. These have comprised laboratory workers, students, and patients suffering from various minor ailments, but in whom clinical examination revealed no abnormality of the circulatory system. In view of the urgent need for a simple quantitative method for the estimation of circulation rate in patients suffering from cardiac disease, we have studied the factors producing variations, more with the object of their elimination, than for the assessment of their quantitative effects in normal individuals. Thus we may determine what standard conditions must be maintained in order to obtain comparable results in patients in the various stages of cardiac disease.

It seems probable that, owing to the effects of various physical and psychological causes, the circulation may vary appreciably from hour to hour or even from minute to minute. In some individuals this instability may be very marked and may be indicated by such simple signs as blushing, blanching, alterations in pulse-rate, palpitation, &c. With the ethyl iodide method variations from such causes will be more apparent because the estimation is completed within the space of a few minutes, whereas with other methods the time required is longer, and any given result is therefore more of an average value.

In the first place it may be asked, What effect, if any, may ethyl iodide itself have upon the circulation and metabolism? From the equation given above it can be seen that, pharmacologically, the effect of ethyl iodide is similar to that from the administration of an equivalent amount of sodium iodide. The amount of alcohol formed is so small and so widely distributed in the blood and tissues as to be negligible. Iodine, however, is a substance of high atomic weight, and the amount absorbed in a single experiment may be equivalent to 0.2 to 0.5 gm. (3-8 gr.) of sodium iodide. Except in an unusually susceptible subject the amount absorbed in one or two consecutive determinations can scarcely be sufficient to cause any appreciable disturbance. On the other hand, there may be considerable disturbances where a number of repeated estimations are made on a single individual in the space of, say, three to four hours. This is rather strikingly shown in the results plotted in Fig. 1. In the case of the subjects W. O. and G. T. the estimations were mostly made on different days. In the case of W. O. four of the observations were made on the one day, two in the morning, and two in the afternoon with a considerable interval between. In these two individuals it can be seen that, apart from slight variations, the circulation rates plotted against the rates of oxygen consumption show almost linear relationships, and that in the case of W. O. an increase of 1 litre per minute in circulation rate is associated with an increase of 56 c.c. per minute of oxygen consumption. In the case of G. T. a similar increase in circulation

is associated with an increase of 44 c.c. per minute of oxygen consumption. In the cases of W. R. and J. H. C., however, in each of whom a series of observations was carried out on one day, there is a steady fall in oxygen consumption and circulation rate, and the latter fall is much greater than the former. In the case of W. R. a fall of 2 litres in circulation rate is associated with a fall of 26 c.c. in oxygen consumption per minute, or 13 c.c. for 1 litre, while in the case of J. H. C. a similar fall in circulation is associated with a fall of 22 c.c. or 11 c.c. for 1 litre. Thus it can be seen that in the case of W. R. and J. H. C., for

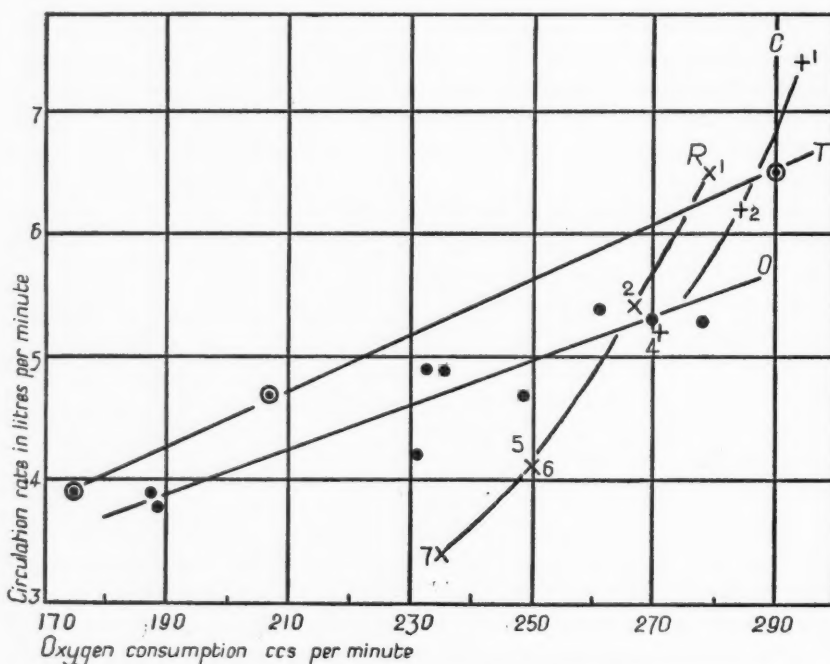


FIG. 1. Circulation rate (litres per minute) plotted against oxygen consumption (c.c. per minute).

Line 0.. = W. O. on different days.
Line T = G. T. on different days.

Curve R x = W. R. on 28.8.26.
Curve C + = J. H. C. on 9.9.26.

In the latter two curves the points are numbered consecutively.

a given fall in oxygen consumption, the fall in circulation rate is approximately four times as much as in W. O. and G. T. In the case of W. R. seven determinations were made in the space of about three hours. These are shown by the numbers in the diagram. Nos. 3 and 4 were not plotted, as in No. 3 there was a technical hitch and the resulting disturbance appeared to produce an abnormally high result in No. 4. No. 7 was completed at 1.05 p.m., the subject feeling somewhat depressed and a little dizzy, but able to enjoy his usual lunch. In the late afternoon and evening, however, marked classical symptoms of iodism developed and persisted for about twenty-four hours. In the case of J. H. C. there was a slight feeling of 'dopiness' at the end of the

series, but no symptoms of iodism developed. In many other subjects a feeling of drowsiness and a fall in circulation rate have been noted after repeated experiments at one sitting, but symptoms of iodism have not been observed except in the case mentioned above. This fall is by no means constant. Examination of the tabulated results shows a number of instances in which duplicate determinations taken with only a short interval give results which agree closely. See, for example, Nos. 4 and 5 on A. R. G., Nos. 7 and 8 on the same subject, also Nos. 87 and 88 on R. V. C. The explanation of the fall in circulation rate after repeated determinations seems rather difficult. Is it a fall which would occur naturally with prolonged rest? This cannot be the case, because in J. H. C. heavy muscular work was performed in the interval between observations 2 and 4. Secondly, it may be due to systematic error—there may be a slight but increasing accumulation of unhydrolysed ethyl iodide in the blood which would make the alveolar concentration too high and the circulation rate consequently too low. This supposition seems to be precluded by the experiments of Henderson and Haggard, but further confirmation seems desirable. Lastly, and perhaps most probably, the accumulated iodide may have a depressant effect—more marked on the circulation rate than on the metabolism. Another possibility must also be considered. From the experiments of Henderson and Haggard it is known that an appreciable time is required for the hydrolysis of ethyl iodide in the blood. Although the mixed venous blood returning to the pulmonary circulation may contain no appreciable quantity of the unchanged substance, yet blood passing to the left heart, and therefore to both coronary arteries, will contain an appreciable amount of unhydrolysed ethyl iodide. This may have a similar depressant effect upon the heart as the other drugs (ethyl chloride and ethyl bromide) of the same series. For our present purposes, however, we may state that from whatever cause, repeated observations at short intervals on the same day on a single individual are liable to be fallacious.

It is important to determine whether in different individuals the circulation rate bears any constant relationship to body size—height, weight, or body surface. In our own series few of the estimations have been made under basal conditions, and there have been a considerable number of circumstances which may have produced variations. Excluding those observations where there have been wide differences, due to fairly obvious causes, we have in Fig. 2 plotted the mean values for circulation rate for 12 individuals (10 males and 2 females) based upon 74 estimations, against the body surface area (from the Dubois height-weight formula). In each individual the extent of the mean deviation is shown by a vertical line. Although in a large series of observations taken under rigidly standardized conditions there may possibly be found some relationship between circulation and body size, allowance being made for age, sex, and bodily habits, yet in the present series it is immediately apparent that there is no such relationship. This supports the conclusion of Field, Bock, Gildea, and Lathrop (5), based upon forty experiments upon twenty-one normal individuals and by a different method, that 'No correlation between the volume of the blood-flow and

any other factor, such as type of build or athletic ability, is apparent'. Hence we are at present unable, except within very wide limits, to predict what should be the normal circulation rate of any given individual, and we may state that at present the clinical value of circulation rate and its estimation is limited to the study of changes in a given individual over different days, after various therapeutic measures, and in different stages of the disease. It may be presumed, however, that fluctuations in circulation rate, which seem to occur in normal individuals, would not occur in cases of severe cardiac disease where the response of the heart is maximal and limited by its functional capacity.

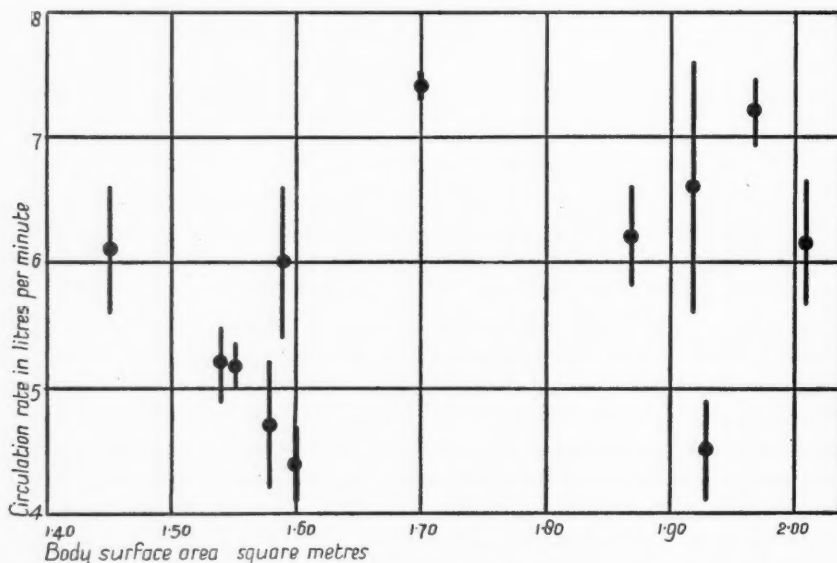


FIG. 2. Average circulation rates in twelve individuals plotted against body surface areas. The magnitude of the mean deviation of each individual is indicated by the vertical lines.

That consistent results can be obtained in a given individual is shown by the fact that in the nineteen observations on A. R. G. the average value was 6.13 with a mean deviation of 0.48, this in spite of the fact that oxygen consumption varies from 260 to 406 c.c. per minute and environmental temperature from 15.5° to 21° C. In the experiments where the deviation was greater than the mean a ready explanation may be found—insufficient preliminary rest, or the depressant effect of a large dose of ethyl iodide. Similarly, in other subjects (for example, W. O. and G. T.) variations in circulation rate are associated with parallel variations in oxygen consumption.

Investigations upon the effects of alterations in metabolism and of previous muscular work upon blood-flow have been hampered by the steady fall in the resting circulation rate during repeated experiments discussed above. It appears, however, that after muscular work the increase in circulation rate continues for a longer period than the increase in metabolism. This is illustrated by Fig. 3,

in which metabolism and circulation rate of a single individual are plotted over a period of 420 minutes. The subject (H. W. D.) rested for 60 minutes before the first determinations were made, and thereafter remained lying comfortably until four observations had been made (in the course of 250 minutes) on blood-flow and the corresponding oxygen consumption. From the figure a fairly close relationship can be seen to exist between the two, except in the case of the third experiment which will be referred to later. Exercise, which included running upstairs three times, was taken over a period of forty minutes. Two further determinations of metabolism and circulation rate were then made. It seems obvious from the figure that the muscular exertion has upset the close relation-

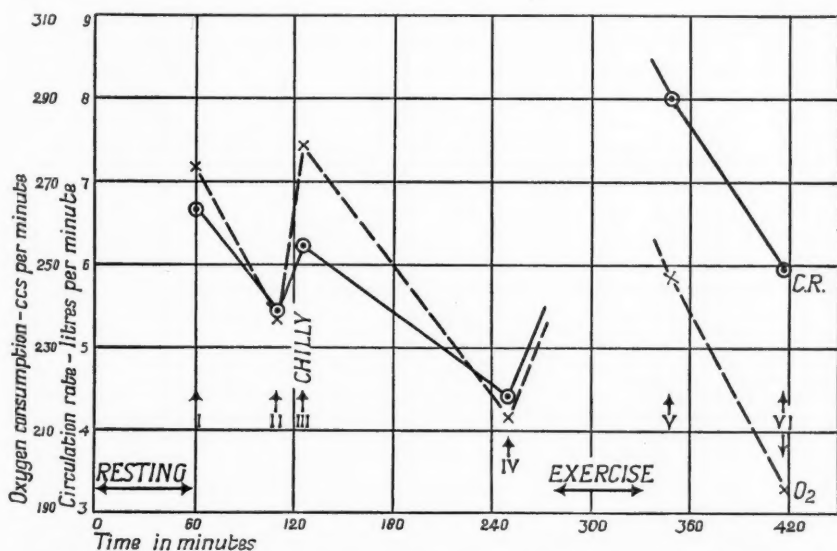


FIG. 3. Shows the relation between circulation rate and oxygen consumption over a period of 420 minutes in subject H. W. D. (Experiments 30-5). Exercise has upset the close relationship which previously existed. The effect of chilling of the body surface is illustrated by the third observation.

C.R. = circulation rate. O₂ = oxygen consumption.

ship which formerly existed between the rate of blood-flow and the O₂ consumption of the tissues. If the exertion be at all prolonged or severe, the metabolism tends to return to the resting value before the circulation rate. Moreover, this effect of exercise may be actually greater than demonstrated, owing to the depressant effect of repeated administrations of ethyl iodide on the circulatory system, as discussed above. From this and other evidence we conclude that previous exercise, even of a minor degree, may be an important factor in disturbing the otherwise fairly close relationship between blood-flow and metabolism in a given individual. At least one hour must elapse after even slight exertion before a true resting value of circulation rate can be obtained.

Recent observations by Field and Bock (9) on the effect of posture on the

rate of blood-flow show that the circulation rate is less in the upright than in the reclining position, and this was accompanied by a great reduction in the output of the heart per beat in the erect position. Similar findings have been reported by Henderson and Haggard using the ethyl iodide method. It seems to us, however, that before definite conclusions can be reached on the effect of posture on the circulation rate, careful control of metabolism throughout the experiments is required. There is another possible source of fallacy suggested to us by J. S. Haldane (personal communication). That is whether in certain subjects in the supine position a true average sample of alveolar air can

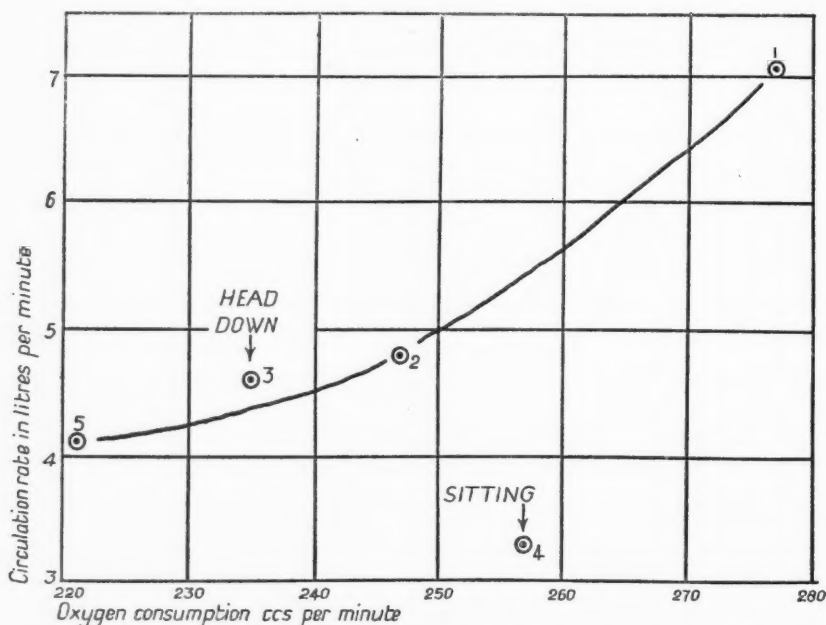


FIG. 4. Shows relation between the circulation rate and oxygen consumption in J. D. R. (Experiments 64-8). Observations are numbered consecutively. Nos. 1, 2, and 5 were made with the subject lying; No. 3 in the Trendelenburg position; No. 4 sitting. For a given metabolism the circulation is lower in the sitting posture, and higher in the head-down position, than with the subject lying flat.

always be obtained. Taking the average values on the series of observations on A. R. G., the ten estimations in the supine position show an average value of 6.26 ± 0.47 litres per minute, while the mean value for nine estimations sitting is 5.98 ± 0.47 . Thus it can be seen that the difference between the two average values is less than the mean deviation for each value. On the other hand, in Fig. 4 we have plotted circulation rate against oxygen consumption in a series of consecutive determinations in the case of J. D. R. It can be seen that the three observations in the supine posture fall on a curve somewhat similar to those in Fig. 1 for W. R. and J. H. C. In the fourth observation the subject was sitting upright, and it can be seen that, for a given oxygen consumption, the

circulation is much less than in the other observations. That this was not due to the possible depressant effect of ethyl iodide is shown by the fact that the subsequent determination (No. 5) showed a higher rate of blood-flow with a lower metabolism. On the other hand, in an observation taken with the subject tilted into the Trendelenburg position, the circulation was slightly greater for a given metabolism. On account of the fluctuations in metabolism it is impossible to draw definite conclusions in the case of J. F., in whom wide variations in the circulation rate occurred with alterations in posture. The position of the subject is therefore an important factor, and in a series of observations on a given patient the posture should be kept constant in order that comparable results may be obtained.

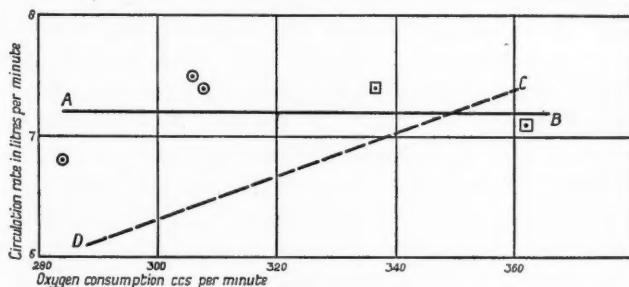


FIG. 5.

D. M. D. ○ on 13.7.26, T. 23.5°-25° C.

□ on 20.7.26, T. 18°.

The line A B gives approximately the relation between oxygen consumption and circulation rate for these five estimations. The line C D has the same slope as that for W. O. in Fig. 1. It can be seen that the estimations on 13.7.26 are higher than can be accounted for by the oxygen consumption.

In discussing the effect of metabolism on the rate of blood-flow, attention was directed to Fig. 3, in which, while the subject lay at rest, the close relationship between the two is clearly shown. This state of affairs is, however, upset in the case of the third experiment in the figure. During the time that this observation was in progress, the subject (H. W. D.) began to feel cold. He remained at absolute rest and no shivering occurred. It will be noted that the result of chilling of the body surface has been an increased oxygen consumption per minute with a smaller proportionate increase in the circulation rate. This is accompanied by an increased output of blood from the heart per beat (Experiment 32). Similar findings are recorded in Experiments 82 and 83 (subject J. H. C.). It seems probable that a slight rise in temperature may be accompanied by the opposite effect. This is shown by the results obtained on the subject D. M. D. (Experiments 114-18) and plotted in Fig. 5. Three observations were made on 13.7.26 when the temperature in the room varied from 23.5° to 25° C. The subject felt so uncomfortably warm that it was necessary for him to remove some of his clothing. The average of the three determinations was 7.23 litres per minute, and the average oxygen consumption

was 300 c.c. per minute. On 20.7.26 with a room temperature at 18° C. the average circulation rate was 7.25 litres per minute and the oxygen consumption 349 c.c. per minute. Thus it may be seen that for a given oxygen consumption the rate of blood-flow is greater when the temperature is higher. These conclusions are in accordance with ordinary naked-eye studies of the cutaneous circulation. It is therefore of some importance, throughout a series of determinations of the circulation rate in the same individual, that chilling of the body surface should not take place, that draughts be avoided, and that the room temperature be uniform and agreeable to the subject.

It is well known that great fluctuations in heart-rate may readily be produced in certain subjects by quite trivial causes. Such disturbing factors as excitement, apprehension, a sudden or unexpected sound, the presence of a stranger, may all profoundly influence the heart-rate, and consequently the blood-flow and the output of the heart per beat. Many subjects unaccustomed to respiratory experiments have shown a greater circulation rate at the first than at subsequent determinations, though at the time of observation they might betray no outward signs of nervousness. Such findings were noted repeatedly, and examples may be found in the case of J. D. R. (Experiments 64 and 65) and A. A. (Experiments 110 and 111). In the latter subject with a steady metabolic rate the first observation gave a reading of 9.0 litres per minute, whereas forty minutes later the blood-flow had fallen by 2.1 litres with an almost similar oxygen consumption. This fall in circulation rate is apparently accompanied by a decrease in the output per beat. Such a reaction, arising from psychological causes, doubtless depends upon the degree of the stimulus and the functional integrity of the heart-muscle. In the great majority of subjects, the first observations are apt to be fallacious, and in the subsequent determinations it is essential that precautions be taken to ensure that the patient is shielded from all emotional disturbances, however trivial. Silence should be maintained and onlookers excluded during the period of observation. A comfortable position with all the muscles relaxed and at ease is essential. In this connexion it is well to make certain before the experiment commences that the nose-clip fulfils its purpose without irritating the subject.

With a view to determining the work of the heart, arterial blood-pressure records have been made in certain subjects. The volume of blood pumped per minute multiplied by the pressure gives the work performed by the heart. In the case of B. M. (Experiment 51) under basal conditions the rate of blood-flow through the heart was 5.3 litres per minute, and the blood-pressure (systolic) 119 mm. Hg. Such a pressure corresponds to a column of blood 1.607 metres high ($119 \times 13.5 = 1606.5$), and consequently the amount of work performed by the left side of the heart equals 8.5 kilogrammetres per minute ($1.607 \times 5.3 = 8.516$). The pressure in the right side of the heart is about one-third that in the left, so that under basal conditions the work of the whole heart in this individual amounted to 11.35 kilogrammetres (82 foot-pounds) per minute, or 1/400 horsepower.

Summary and Conclusions.

1. The ethyl iodide method of estimating circulation rate possesses many advantages over methods hitherto in use. Determinations can be carried out in a few minutes and produce no discomfort or disturbance to the subject. The results are reasonably consistent provided constant conditions are maintained and errors of technique are avoided.

2. Various slight technical modifications are suggested, the most important of which are—first, the substitution of red-lead coated flexible metal tubing in place of rubber tubing in the breathing circuits, and secondly, the use of valves which produce no resistance or other disturbance to respiration.

3. A table is given showing the findings in 118 determinations in eighteen individuals under various conditions as regards posture, temperature, activity, and metabolism.

4. Excessive amounts of ethyl iodide appear to have a depressant effect upon the circulation rate in certain individuals. For this reason repeated estimations over too short a period are liable to be fallacious.

5. In the present series of observations there is no relationship between circulation rate and any other physical measurements in different individuals.

6. Considerable variations in circulation rate may be associated with varying conditions of metabolism, activity, environmental temperature, posture, and emotional excitement. For this reason the conditions under which observations are made on any given subject must be carefully standardized in order that comparable results may be maintained.

We wish to express our thanks to the Medical Research Council for their generous assistance. We are also indebted to various colleagues and others who acted as subjects. The patients upon whom estimations were made were from the wards under the charge of Professor D. Murray Lyon. Dr. W. Robson and Mr. J. D. Robertson, B.Sc., gave us advice and help on various chemical matters. Our technical assistant, Mr. John Flett, helped us in the analysis of many of the samples.

The large 200-litre spirometer was supplied by Messrs. James Milne & Son, Ltd., Edinburgh, and we are indebted to them for their courtesy and help. The electrically heated oven was made for us by Messrs. Melville & Hunter, Edinburgh.

H. W. D. (continued)	27	19.8.26	5.7	84	68	6.54	255	20° C.	Lying	
	28	"	5.4	71	76	6.92	252	20	"	Without lunch. B.P. 118/86. Atropin gr. $\frac{3}{32}$ 15 min. before. 3.28 p.m.
	29	23.8.26	9.3	136	68	6.88	296	17.5	"	Without lunch. B.P. 123/92. Atropin gr. $\frac{3}{32}$ 30 min. before. 3.44 p.m.
	30	5.9.26	6.7	100	67	6.72	273	17.5	"	Before lunch. 1.1 p.m. Very light breakfast. Taxi to lab. Rested 60 min. B.P. 122/74. Coughing during determination. 11.10 a.m.
	31	"	5.4	94	58	6.44	237	17.5	"	Lying on left side. B.P. 123/76. More comfortable. No coughing. 11.50 a.m.
	32	"	6.2	109	57	7.04	282	17.5	"	Feeling chilly. 12.14 p.m.
	33	"	4.4	82	54	6.42	253	17.5	"	Still on left side. Blanket. Dozing. 2.19 p.m.
	34	"	8.0	127	63	7.80	249	17.5	"	11 min. after running 3 times upstairs. 3.57 p.m.
	35	"	6.0	109	55	6.12	196	17.5	"	80 minutes after. 5.7 p.m.
	36	6.9.26	5.6	84	67	6.39	250	17.2	Sitting	No lunch. 3.49 p.m.
	37	8.9.26	9.2	113	81	8.42	352	18	"	After lunch. Felt arterial pulsation. 2.44 p.m.
	38	"	8.0	107	75	7.56	287	18	"	After lunch. 4.30 p.m.
W. O. Ht. 164 cm. Wt. 55 kg. Surface 1.58 sq. m. Aged 27. Labourer. Dropped foot. Circulation clinically normal	39	19.7.26	6.2	87	71	9.42	279	19	Lying	After breakfast (?slightly apprehensive). 10.40 a.m.
	40	"	5.3	82	65	7.65	278	19	"	After breakfast. 11.30 a.m.
	41	"	4.7	75	62	6.38	249	19	"	" " 12.40 a.m.
	42	29.7.26	5.4	85	63	7.32	261	19	"	" " 10.17 a.m.
	43	30.7.26	4.2	71	59	5.88	231	20	"	Fasting. 10.20 a.m.
	44	31.7.26	4.9	83	59	5.67	233	19	"	" " 9.40 a.m.
	45	2.8.26	3.9	64	61	4.65	188	20	"	" " 10 a.m.
	46	"	3.8	64	60	4.85	189	20	"	" " 10.35 a.m.
	47	"	5.3	71	74	6.02	270	20	"	After lunch. 2.50 p.m. Light lunch. Finished at 1.40 p.m.
	48	"	4.9	69	70	5.80	235	20	"	After lunch. 3.35 p.m. Light lunch. Finished at 1.40 p.m.

Name, Height, and Weight.	Experi- ment No.	Date.	Circula- tion Rate, Litres per Minute.	Output per Beat, c.c.	Pulse- rate.	Respira- tory Minute Volume, Litres.	Oxygen Consump- tion, c.c. per Minute.	Tempera- ture (Room).	Posture.	Remarks.
B. M. Ht. 152 cm. Wt. 63 kg. Surface 1.59 sq. m. Aged 22. Medical student. Small build. Ath- letic	49	10.8.26	7.9	78	102	7.04	346	18° C.	Lying	After lunch (? nervousness). 3.5 p.m. Walked to lab. 10.38 a.m. B.P. 118/94
	50	11.8.26	6.0	88	68	5.00	244	17.5	"	Fasting. B.P. 118/94
	51	"	5.3	85	62	4.74	?	17.5	"	Fasting. 11.15 a.m. B.P. 119/92
	52	"	4.8	79	61	4.60	215	17.5	Head down	" 11.58 a.m. B.P. 121/90
	53	"	4.0	67	60	5.17	226	17.5	Sitting	" 12.37 p.m. B.P. 122/93
	54	17.8.26	7.0	111	63	5.79	263	20	Lying	About 1 hr. after light break- fast. 9.45 a.m. Walked to lab. B.P. 122/80
	55	"	6.4	93	69	5.92	276	20	"	Smoked cigarette just before. 10.25 a.m. B.P. 123/81
	56	20.8.26	7.6	114	67	7.01	292	16	"	After breakfast. Hurried to lab. 10.12 a.m.
	57	24.8.26	9.4	122	77	6.58	295	20	"	After breakfast. Walked to lab. Only 15 min. rest. 10.3 a.m.
	58	"	7.5	94	79	6.26	267	20	"	Same morning. 10.37 a.m.
J. F. Ht. 165 cm. Wt. 57 kg. Surface 1.61 sq. m. Aged 18. Lab. techni- cian. Small build	59	"	6.7	95	70	5.92	243	20	"	" 11.16 a.m.
	60	"	5.9	87	68	5.78	250	20	"	" 11.55 a.m.
	61	8.7.26	5.5	75	73	5.58	242	17	Sitting	Sinus arrhythmia. After break- fast. Not rested sufficiently
	62	"	3.6	46	78	5.85	238	17	Standing	After breakfast. Not rested sufficiently
	63	10.7.26	7.0	84	83	6.21	313	20	Lying	After breakfast. Walked to lab. Running messages
	64	21.7.26	7.1	102	69	7.37	277	19	Lying	Soon after arrival. Walked to lab. 10.40 a.m.
	65	"	4.8	74	65	6.66	247	19	"	11.15 a.m.
	66	"	4.6	78	59	7.20	235	19	Head down	11.55 a.m.
	67	"	3.3	53	62	7.26	257	19	Sitting	12.35 p.m. On hard chair.
	68	"	4.1	72	57	6.12	221	19	Lying	1.5 p.m. After lunch. 2.44 p.m. B.P. 116/63
69	14.8.26	5.9	94	63	7.40	282	?	?	"	116/63
70	"	4.1	69	60	6.78	245	?	?	"	After lunch. 3.25 p.m. B.P. 117/62

W. R. Ht. 179 cm. Wt. 66 kg. Sur- face 1.82 sq. m. Chemist. Slight build. Moderately sedentary. Aged 32	71 72 73 74 75	28.8.26 " " " "	6.5 5.4 4.1 4.1 3.4	91 83 75 77 65	72 65 55 53 53	7.86 7.45 6.82 6.90 6.65	279 267 250 250 235	18.5° C. 18.5 18.5 18.5 18.5	Lying " " " "	9.58 a.m. Only 15 min. rest 10.38 a.m. B.P. 107/69 11.54 a.m. B.P. 106/69 12.29 p.m. B.P. 106/69 1.5 p.m. Dozing. B.P. 106/68 Subsequent iodism
J. H. C. Ht. 174 cm. Wt. 59 kg. Surface 1.70 sq. m. Physi- cian. Moderately sedentary. Aged 32	76 77 78 79 80 81 82 83	1.9.26 " " 9.9.26 " " " "	7.3 7.5 8.6 7.4 6.2 8.2 5.2 5.9	99 105 115 119 101 80 69 90	74 71 75 62 61 103 76 65	6.29 6.31 6.47 6.61 6.38 10.40 6.74 6.58	274 272 303 294 284 372 271 330	15 15 15 16.5 16.5 16.5 16.5 16.5	Sitting " " Lying " " " "	12.3 p.m. Before lunch 12.35 p.m. " " 3.45 p.m. After " " Light breakfast. Taxi to lab. 45 min. rest. 10.15 a.m. 10.51 a.m. " " 11.44 a.m. 15 min. after exer- cise 12.21 p.m. " " 1.12 p.m. Feeling cold
R. V. C. Ht. 180 cm. Wt. 75 kg. Sur- face 1.98 sq. m. Resident physician. Aged 24. Active	84 85 86 87 88 89 90 91 92	9.8.26 18.8.26 " 13.9.26 " " " " "	3.6 6.2 6.4 4.7 4.7 15.2 4.0 5.1 3.9	72 109 113 88 85 136 65 91 72	50 57 57 53 55 112 61 56 54	5.91 8.03 7.82 5.92 6.86 37.40 7.00 6.76 7.08	242 384 314 269 249 2132 346 288 319	? 19 19 16 16 16 16 16 16	Lying " " " " Sitting Lying " "	Fasting. 9.45 a.m. Resting 45 min. After lunch (+ beer). 2.27 p.m. B.P. 116/78 After lunch. 3.1 p.m. B.P. 113/76 No lunch. After 60 min. rest. 2.18 p.m. A little restless. 2.46 p.m. On ergometer, pedalling. 3.12 p.m. Dozing. 3.40 p.m. 4.12 p.m. Uncomfortable 4.40 p.m.
G. T. Ht. 161 cm. Wt. 61 kg. Sur- face 1.63 sq. m. Constipation. Cir- culatory system normal. Aged 46	93 94 95	24.6.26 25.6.26 28.6.26	6.5 4.7 3.9	82 73 57	80 64 69	7.61 5.49 5.20	290 207 175	16 16 16	Lying " "	After breakfast. Nervous. 9.45 a.m. After breakfast. 10.50 a.m. " " 10.30 a.m.

Name, Height, and Weight.	Experi- ment No.	Date.	Circula- tion Rate. Litres per Minute.	Output per Beat. c.c.	Pulse- rate.	Respira- tory Minute Volume. Litres.	Oxygen Consump- tion. c.c. per Minute.	Tempera- ture (Room).	Posture.	Remarks.
Miss F. R. Ht. 159 cm. Wt. 55 kg. Surface 1.55 sq. m. Physician. Moder- ately active. Aged 25	96	16.7.26	6.3	71	88	6.09	244	18.5° C.	Lying	Nervous. Not sufficient rest 11.15 a.m.
	97	"	5.0	65	77	5.64	223	18.5	Head down	12 noon
	98	10.8.26	5.3	78	68	5.38	205	18	Lying	Sleepy. Before lunch. 1.35 p.m.
Miss E. C. Ht. 157 cm. Wt. 55 kg. Surface 1.54 sq. m. Physician. Moder- ately active. Aged 31	99	2.9.26	6.4	86	75	4.52	203	17	Sitting	10.5 a.m. 30 min. rest after walking to lab.
	100	"	4.9	67	73	4.57	210	17	"	11.55 a.m.
	101	"	5.4	79	68	4.34	196	17	"	1.25 p.m.
A. F. Ht. 182 cm. Wt. 68 kg. Surface 1.87 sq. m. Constipa- tion. Normal heart. Iron - moulder, formerly gas in- structor. Aged 30	102	12.7.26	6.5	90	72	6.11	345	22	Lying	Nervous. Not sufficient rest. 10.45 a.m.
	103	15.7.26	6.5	124	52	6.56	256	19	"	11.15 a.m.
	104	"	5.6	115	49	5.46	215	19	Head down	12 noon
W. A. Ht. 178 cm. Wt. 64 kg. Surface 1.80 sq. m. Lab. technician. Moder- ately sedentary. Aged 21	105	6.8.26	7.4	106	70	7.68	315	19.5	Lying	After lunch. 3.20 p.m.
	106	3.9.26	7.8	111	70	7.30	311	18	Sitting	" 30 min. rest.
	107	"	5.7	84	68	8.04	283	18	"	" 2.34 p.m. 3.6 p.m.
W. S. Ht. 155 cm. Wt. 49 kg. Sur- face 1.45 sq. m. Catarrhal jaundice. Normal heart. Ap- prentice. Aged 16	108	13.8.26	6.6	88	75	7.66	306	18	Lying	After breakfast. 10.55 a.m.
	109	"	5.5	77	71	7.46	278	18	"	11.37 a.m.

A. A. Ht. 169 cm. Wt. 80 kg. Surface 1.90 sq. m. Rheu- matoid arthritis. Normal heart. En- gine driver. Aged 43	110	18.8.26	9.0	117	78	7.18	307	19° C.	Lying	Fasting. 9.45 a.m. ? appre- hensive
	111	"	6.9	95	73	6.95	300	19	"	Fasting. 10.25 a.m.
C. M. Ht. 170 cm. Wt. 55 kg. Surface 1.62 sq. m. Oxal- uria. Normal heart and circula- tory system. Fire- man. Aged 25	112	26.8.26	4.8	62	77	5.50	233	17.5	"	Walked from ward. 25 min. rest. 9.47 a.m.
	113	"	4.8	72	66	5.67	230	17.5	"	10.29 a.m.
D. M. D. Ht. 187 cm. Wt. 73 kg. Surface 1.97 sq. m. Resident physician. Aged 24	114	13.7.26	7.5	119	63	7.06	307	23.5	Lying	After lunch. Walked to lab.
	115	"	7.4	125	59	7.17	308	24	Head down	" "
	116	"	6.8	113	60	7.85	284	25	Lying	" "
	117	20.7.26	7.1	113	63	9.03	362	18	"	" 3.10 p.m.
	118	"	7.4	114	65	8.84	336	18	"	3.40 p.m. Slightly restless

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FRACTIONAL ANALYSIS OF THE GASTRIC CONTENTS

A PRELIMINARY NOTE ON THE VARIATION OF THE FREE HYDROCHLORIC ACID AND TOTAL CHLORIDES IN THE UPPER AND LOWER PARTS OF THE STOMACH¹

By ROBERT J. DUTHIE

(From the Tor-na-Dee Sanatorium)

THE fractional method of gastric analysis has been subjected to so much criticism recently that it is evident that there must be some cause for the variation in the results obtained, and, consequently, for the diversity of opinion as to the value of the test as compared with the simple Ewald test meal.

Bell and MacAdam (1) noted that, if a fractional test meal is performed on the same patient on several successive days, marked variations are found in the acidity of the gastric contents. I have made a similar observation, and have even found that a normal acidity curve on one day may give place to a curve showing complete absence of free acidity on the following day. When it is remembered that the absence of free hydrochloric acid is a point of importance in the diagnosis of pernicious anaemia, &c., it is necessary to eliminate the possibility of error regarding the gastric acidity.

Gorham (2) in 1921 emphasized in a different way the importance of variation of test-meal samples. He removed the whole of the stomach contents, forty-five minutes after giving a test meal, in 10 c.c. portions, and found that these consecutive samples showed definite variations in acidity in most cases.

One cause for the variation in the findings is that the gastric contents often vary at different parts of the stomach at any particular time during the test. Butcher (3), by withdrawing his stomach tube, noted a difference of ten points between the acidity of the pyloric end of the stomach and that of the fundus, but he considered the ordinary fractional analysis gave a 'fair indication of the changes of acidity during digestion, provided the level of the tube is kept constant during the meal'.

Baird, Campbell, and Hern (4), and Lim, Matheson, and Schlapp (5), described experiments in which two separate tubes were passed, one into the duodenum, and the other into the stomach. The former observers made simultaneous estimations of the duodenal and gastric acidity at definite intervals during the digestive cycle. The latter made experiments regarding the response of the stomach to histamine by using similar technique.

¹ Received September 30, 1926.

It also occurred to me that information might be gained by obtaining, by the fractional method, samples of the gastric contents at different levels in the stomach simultaneously, and the following experiments were undertaken to determine what differences, if any, existed in the acid and chloride concentrations in samples thus obtained.

Description of Experiments.

It was necessary for the experiments to make a two-way stomach tube to obtain simultaneous samples of the gastric contents from the two parts of the stomach. To an ordinary Ryle tube, a tube of similar diameter and bore was sutured about eight inches from the bulb, and at short distances along the lengths of the tubes. A double stomach tube was thus obtained, the openings of which were eight inches apart, and rather less than this when the tubes lay *in situ* along the greater curvature. The patients were examined in the sitting posture throughout the experiments, and during the radiological examinations when necessary to determine the position of the tubes. The latter were not moved in any way after the test meal was given.

The procedure after swallowing the tubes was the same as that of an ordinary test meal, except that two series of specimens of the gastric contents were obtained, one from the longer Ryle tube, and the other from the shorter attached tube. The specimens from the longer tube were removed from the pyloric region of the stomach, and those from the shorter tube seven or eight inches nearer the cardiac region.

Description of the Findings in three Cases.

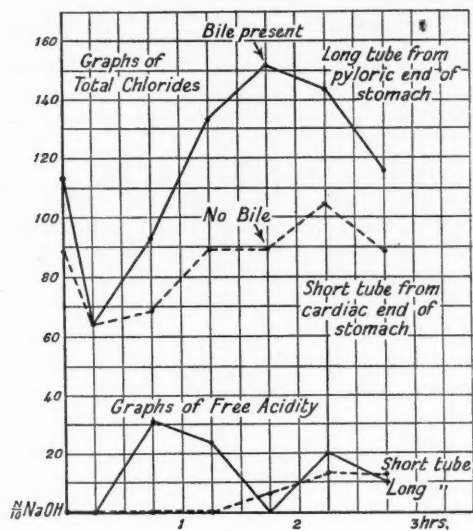
Case No. I. A sample of the resting secretion was obtained from both tubes. The usual test meal of gruel was given, samples of the gastric contents being aspirated a quarter of an hour later, and then at half-hourly intervals. The graph shows the curves of the amounts of free acid and total chlorides found in the specimens.

Free acidity from the longer tube was demonstrated after three-quarters of an hour, whereas it could be demonstrated only after $1\frac{1}{2}$ hours from the shorter tube.

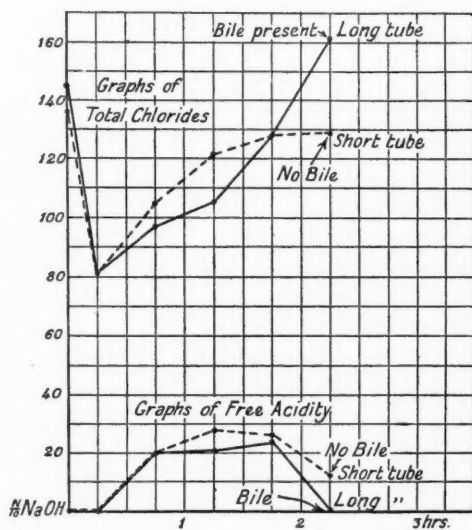
Bile was withdrawn from the longer tube $1\frac{1}{2}$ hours after the meal, but there was no trace of bile in any sample from the shorter tube. By screening the patient the possibility of the longer tube being in the duodenum was eliminated, so that it could be safely assumed the bile was regurgitated from the duodenum.

After the effect of the alkaline regurgitation had passed, there was again a rapid rise in acidity in the pyloric region, while the acidity nearer the cardiac region continued to rise more gradually. It will be noticed in this case that the alkaline duodenum secretion had a profound effect in neutralizing the acidity in the pyloric part of the stomach, although nearer the cardiac region it seemed to have little or no effect.

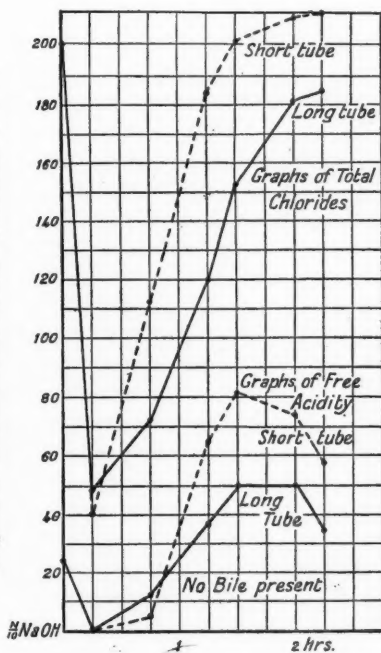
Case No. II. The accompanying graph shows the relation of the acidity and chlorides in the second case. Unlike the previous one, the higher curves (both the acidity and chlorides) were obtained from the shorter tube. This graph, like the previous one, shows the effect of duodenal regurgitation. Bile was seen in



CASE I.



CASE II.

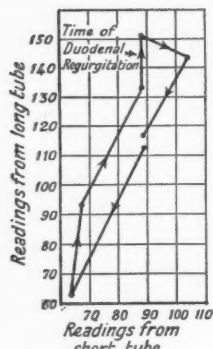


CASE III.

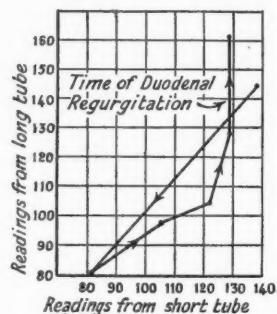
the specimen from the long tube $2\frac{1}{4}$ hours after the test meal was given. The patient was screened, and all possibility of the tube being in the duodenum eliminated. The acidity in the pyloric portion of the stomach was reduced to zero, and the total chlorides rose simultaneously. It will be noted that in this case also, the sample from the higher part of the stomach was reduced only very little by the regurgitation of bile, and there was no marked rise in the total chlorides from the short tube.

Case No. III. This graph shows the curves found in a case of hyperchlorhydria. In this instance, however, the whole of the resting contents of the stomach was removed (about 60 c.c.) before the gruel was given. In the previous two cases only 4 c.c. of the resting secretion were aspirated. It will be noticed in this graph that the higher curves of free acid and chlorides were obtained from the upper part of the stomach. There was no sign of regurgitation of bile during the test meal.

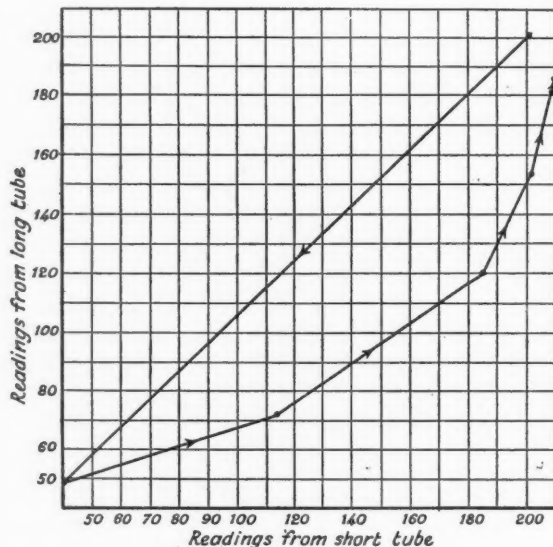
In the following three graphs the readings of the total chlorides from the



CASE I.



CASE II.



CASE III.

upper part of the stomach have been compared with those from the lower part by plotting the former as abscissae, and the latter as ordinates. These graphs roughly indicate the varying differences of the total chlorides at two different points in the stomach during the course of the fractional test.

Summary.

A method of obtaining simultaneously samples of gastric contents at two points has been described, and the variations of the free acidity and total chlorides have been compared in three cases.

Differences in the free acid and total chlorides were found in the upper and lower regions of the stomach during the digestive cycle in three cases.

In Case No. I the greatest difference in the free acidity was found to be 31 units (in terms of N/10 NaOH, *vide* graphs), occurring $\frac{3}{4}$ hour after the test meal, and in the total chlorides 63 units, occurring $1\frac{3}{4}$ hours after the meal, i. e. simultaneous with the duodenal regurgitation.

In Case No. II the greatest differences were 12 units in acidity, $2\frac{1}{4}$ hours after the meal, and 32 units in total chlorides, also $2\frac{1}{4}$ hours after, and simultaneous with regurgitation.

In Case No. III 33 units was the greatest difference in acidity, $1\frac{1}{2}$ hours after the meal, and 65 the greatest in total chlorides, $1\frac{1}{4}$ hours after the meal. No regurgitation was noted.

Duodenal regurgitation was shown to affect the gastric contents chiefly in the lower part of the stomach.

The graphs illustrate how the findings in a fractional test meal partly depend on the position of the tube in the stomach.

This method of gastric analysis is very laborious, but it gives much more information than the ordinary fractional method, and its more extended use might help to elucidate some of the physiological and pathological problems of the digestive process.

My thanks are due to Dr. J. M. Johnston for facilities afforded me in Torna-Dee Sanatorium, and to Dr. William F. Croll for kindly permitting me to investigate Case No. III at the Aberdeen Royal Infirmary. I wish to acknowledge much helpful advice from both.

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AN INVESTIGATION OF GASTRIC FUNCTION IN CHRONIC ARTHRITIS AND FIBROSITIS¹

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Introduction.

THE objects of the investigation are to establish the incidence of varying grades of gastric acidity in chronic arthritis and allied conditions, and to correlate any association between gastric secretion and the predominance of streptococci in cultures of faeces.

The term chronic arthritis is used in its widest meaning to include fibrositis and osteo-arthritis, because narrow classification is admittedly difficult, the differentiation between non-articular and articular fibrositis and chronic arthritis being frequently vague.

Two hundred and fifty patients have been studied, a large proportion of whom have been in-patients at the Royal Bath Hospital, Harrogate. The only selection made has been the exclusion of cases in which the disease is no longer active, the patients suffering only from crippling sequelae.

Records of gastric analyses in chronic arthritis appear inadequate; the majority are based on the older method of examination by a single sample withdrawn one hour after an Ewald meal of tea and toast, or, if the more modern fractional method of Rehfuess and Hawk (1) has been used, the number of patients examined is small, or the opinions expressed are generalizations without reference to detailed observations.

The subdivision of degrees of acidity is practically the same as that employed by Bell (2), a slight modification of Bennett and Ryle's original classification:

Achlorhydria.	No free HCl in the stomach at any time during the test.
Hypochlorhydria.	Free HCl at no time greater than 10 units.
Normal.	Free HCl at no time greater than 50 units.
Hyperchlorhydria.	Free HCl at some time greater than 50 units.

A unit of HCl is defined as the equivalent of 1 c.c. of N/10 HCl per 100 c.c. of gastric contents.

Table I summarizes the results referred to in the following paragraphs, and compares them with the results in 100 normal subjects obtained by Bennett and Ryle (3) and with 425 cases of general diseases examined by Bell.

¹ Received November 26, 1926.

Woodwark and McKenzie Wallis (4) examined by Ewald's test meal ten cases of rheumatoid arthritis. They refer to the relief of symptoms following the administration by the mouth of 5 minims of ac. hydrochlor. dil. t.d.s., ascribing the result to the bactericidal action of the HCl. So small an amount cannot intrinsically alter the free HCl content of a stomach which contains food.

Faber (5) states that of sixty-five cases of chronic polyarthritis fifteen were associated with absence of free HCl in the Ewald test meal.

TABLE I.
Summary of Previous Records of Gastric Acidity.

<i>Chronic Arthritis.</i>					
		Percentage Incidence of			
	No. of Cases.	Achlor-hydria.	Hypochlor-hydria.	Normal Acidity.	Hyperchlor-hydria.
Woodwark *	10	20	40	—	—
Faber *	65	23	—	—	—
Bell †	13	38	23	14	23
Coates *	20	70	5	25	—
Venables †	8	—	—	50	—
Douthwaite †	30	—	—	90	—
Ashcroft †	50	Large proportion		—	—
<i>Other Diseases.</i>					
Bell †	425	15	12	48	24
<i>Normal Subjects.</i>					
Bennett and Ryle †	100	4	1	87	8

* Ewald test meal.

† Fractional technique.

* Ewald test meal.

† Fractional technique.

In notes on 425 fractional analyses in different diseases, Bell (2) includes eight cases of rheumatoid arthritis and five cases of fibrositis. Although the number of these cases is small, the deviation from normal is marked. In the same communication are records of similar abnormal results in other diseases, e.g. chronic gastritis, the sequelae of gastrojejunostomy and chronic appendicitis. These results are confirmed in general by Bonar (6) and Hurst (7). Bell, Hurst (8), and Coates and Gordon (9), all consider achlorhydria a primary or secondary factor in the aetiology of chronic arthritis.

Wynne (10) considers streptococci isolated from the faeces as a cause of toxaemia, and that HCl taken by the mouth is rational and useful treatment in cases of achlorhydria.

Venables and Knott (11) refer to four cases of rheumatoid arthritis (out of eight examined) as having normal gastric acidity but infected contents of the duodenum. They found that positive cultures from duodenal contents in many diseases occur four times more frequently in the absence than in the presence of free HCl in the stomach. Such a marked predominance is not confirmed by Bartle and Harkins (12), though they find the same tendency.

In disagreement with the general indication of the records already mentioned are the results of Douthwaite (13), who not only considers that achlorhydria is

of no importance in the aetiology of rheumatoid arthritis, but also doubts the accuracy of the assertion that it is frequent.

Ashcroft and others (14) mention achlorhydria and hypochlorhydria as a feature in a large proportion of fifty cases of chronic arthritis.

Rolleston (15) considers that the activity of intestinal bacteria varies with the presence or absence of HCl in the stomach, but indicates the need for further investigation before the toxæmia of intestinal bacteria can be accepted generally as a primary cause of rheumatoid arthritis.

Facts relating to micro-organisms isolated from the faeces of normal subjects or cases of chronic arthritis are not numerous, and there is a prevalent tendency to accept generalized opinion without detailed observation. In practice there are difficulties. Diet, rapidity of peristalsis in the intestines, type of medium used for inoculation, and delay in examining the faeces after the passing of the specimen are all factors which influence the isolation of the micro-organisms, and in the routine examination of patients the two first-named factors are almost beyond practical control. L. P. Garrod (16) has demonstrated the absence of a constant type of intestinal flora in normal individuals.

In aerobic cultures two main types of micro-organisms are found, coliform bacilli and streptococci; less frequently staphylococci and diphtheroid bacilli. There is a general tendency, indifferently supported by evidence, to incriminate streptococci in the faeces as causes of intestinal toxæmia in many disorders, including chronic arthritis and fibrositis. Evidence in support of this opinion should refer to proofs of pathogenicity, the methods of assessing which are still unsatisfactory. If agglutinins or complement-fixing bodies in the serum (Burbank and Hadjopoulos (17)) be accepted as evidence of pathogenicity, then coliform bacilli are potentially as pathogenic as streptococci (Kauntze (18)).

Mutch (19) states that 'infective' streptococci have been recovered from the faeces of 84 per cent. of 200 cases of chronic arthritis. He does not define an infective streptococcus, nor does he suggest that the 84 per cent. incidence is different from that in normal individuals. Streptococci are frequently predominant in the cultures of faeces of apparently healthy subjects.

Willcox (20) states that in over 90 per cent. of cultures from the colon washings of patients with chronic arthritis a 'definite pathogenic infection is found, usually *Streptococcus viridans*'.

In our experience, *Streptococcus viridans* is not found in such predominance, non-haemolytic strains of the faecal type being much more common. Until some more reliable method of assessing the pathogenicity of bacteria is devised, caution should be observed in accepting as pathogenic all and sundry micro-organisms isolated from the faeces.

Method.

The method used in this investigation for the analysis of gastric contents is that described by Ryle (21), based on that originally outlined by Rehfuess and Hawk. The test meal is 45 gm. of oatmeal made to one pint of gruel,

administered after the withdrawal of the fasting contents. Samples are withdrawn for analysis every twenty minutes until the stomach is empty. Free HCl is estimated by titration against Töpfer's indicator, total acidity against phenolphthalein.

The faeces examined are free motions passed after a suitable laxative. Urine is obtained by catheter from women, and from men by a fractional passing into sterile containers after washing up with weak lysol, the last portion passed being used for examination. Media are inoculated with as small a fragment of faeces as possible, with associated mucus if present, and with the centrifugalized deposit of 7 c.c. of urine.

All specimens are inoculated on two types of medium:

1. Glucose bullock's blood-agar as described by Crowe (22).
2. McConkey's medium.

Further identification of streptococci within the three broad groups, non-haemolytic, viridans, and haemolytic, is obtained by subculture on agar plates covered by a thin film of fresh human blood-agar.

Type of Patient.

The series excludes cases associated with specific known infection, such as tuberculosis, gonorrhoea, syphilis, enteric fever, pneumonia, or zymotic fevers, and cases of true gout or of arthritis clearly the result of trauma.

The grouping of the cases is a slight modification of that outlined by Pringle and Miller (23) and at present employed by the physicians of the Royal Bath Hospital, Harrogate.

1. Group A. The chronic disability in this group is apparently the close sequel of a history suggesting acute rheumatic fever. Although the number of cases in this group is small, they are included because clinically they closely resemble the early stage of what in other patients is clearly a chronic arthritis from the beginning.

2. Group B. This group is associated with sepsis, which has been accepted as the cause of the condition. It constitutes about 30 per cent. of the whole.

3. Group C. This group is indeterminate in aetiology and constitutes about 50 per cent. of the whole. There is no clear evidence of sepsis; metabolic defect is frequently pronounced and may be an important factor in aetiology. In general this group corresponds with what is commonly defined as the atrophic type, or, by some, true rheumatoid arthritis.

4. Fibrositis. This group is quite small. The disability is mainly non-articular, occasionally localized around joints, but more often confined to ligaments and fascial sheaths of muscles and tendons.

5. Osteo-arthritis. This group is easily defined because of the proliferative bony changes. It is included because there is evidence that aetiological factors may frequently be the same as in the other groups.

TABLE II.

Sex Incidence in Various Clinical Groups of Chronic Arthritis.

	250 Cases.	Percentage of		
		170 Women.	80 Men.	Total.
Group A	12	5	5	5
Group B	70	28	27.5	28
Group C	127	53	46	51
Fibrositis	26	9	12.5	10
Osteo-arthritis	15	5	9	6

The fact that there are twice as many women as men in the series is in accordance with accepted opinion. It is difficult to refrain from associating such a sex predominance with the greater frequency in women of infection and endocrine disturbance associated with parturition and menstruation. The menopause is frequently related with the onset or aggravation of the disease.

That half of the patients examined are classed in an indeterminate group (Group C) is an index of lack of knowledge of the aetiology of the disease, as well as of the infrequency of the detection of sepsis.

There is a slightly higher percentage of men than women with fibrositis, a discrepancy still more marked in osteo-arthritis. The numbers falling within these two groups are relatively small and scarcely justify generalized conclusions.

TABLE III.

Age Incidence in Various Clinical Groups of Chronic Arthritis.

	Percentage in Age Decades.					
	0-20.	20-30.	30-40.	40-50.	50-60.	60-70.
Group A	41	8	25	25	—	—
Group B	4	21	34	24	17	—
Group C	5	12	31	28	19	5
Fibrositis	—	8	27	34	23	8
Osteo-arthritis	—	7	7	20	46	20

This crippling disease falls heaviest on individuals between 30 and 50 years old. In fibrositis there is a slight, and in osteo-arthritis a marked, tendency for older subjects to be attacked, i. e. after 50 years of age. In women the period of 30 to 50 is that of greatest uterine function. Premature cessation of menstruation in women suffering from chronic arthritis requires investigation, i. e. to what extent it precedes or follows the disease. It is a frequent occurrence.

TABLE IV.

Relationship between Sex and Age in Chronic Arthritis.

Years	0-20.	20-30.	30-40.	40-50.	50-60.	60-70.
Percentage of 170 women	6	16	29	28	16	4
Percentage of 80 men	5	8	30	24	27	6

The incidence of men and women is closely parallel, except (i) between 20 and 30, where there is a predominance of women; this corresponds with the

onset of full uterine activity and the possibility of endocrine disorder and sepsis ; (ii) after 50, when more men than women are affected. This may be explained by greater susceptibility of men to osteo-arthritis, in which trauma and exposure are contributory causes.

Results of Gastric Analysis.

Table V contrasts the analysis of the gastric acidity in the present series of cases with that of 100 normal subjects recorded by Bennett and Ryle, 425 cases of other diseases recorded by Bell, and 100 cases of other diseases seen by the writers.

TABLE V.
Percentage Incidence of Degrees of Gastric Acidity.

No. of Cases.	Clinical Types.	<i>Chronic Arthritis.</i>		Normal Acidity.	Hyperchlorhydria.
		Achlorhydria.	Hypochlorhydria.		
12	Group A	17	—	76	8
70	Group B	11	6	74	9
127	Group C	27	7	60	6
26	Fibrositis	35	7	35	23
15	Osteo-arthritis	13	13	47	27
250	Total	22	7	61	10
<i>Other Diseases.</i>					
100	*Authors	10	2	70	18
425	Bell	15	13	48	24
<i>Normal Subjects.</i>					
100	Normal (Bennett and Ryle)	4	1	87	8

* Excludes Addison's anaemia and carcinoma of the stomach.

Cases of chronic arthritis diverge from normal in the direction of hypochlorhydria and achlorhydria, though only slightly more than in Bell's series of other diseases.

The different groups within the 250 cases show variations in acidity. Groups A and B diverge least from normal, though there is increase of achlorhydria and hypochlorhydria. In Group C there is more frequent achlorhydria. The relatively small group of fibrositis shows the widest variation from normal in both decrease and increase of acidity, a similar variation to a less degree being present in osteo-arthritis. The hyperchlorhydria in these two groups is partly explained by the greater percentage of men.

TABLE VI.
CHRONIC ARTHRITIS.

Percentage Incidence of Degrees of Gastric Acidity in Age Decades.

Age.	250 Cases.	Achlorhydria.	Hypochlorhydria.	Normal Acidity.	Hyperchlorhydria.
10-20	14	14	7	71	7
20-30	34	17	9	73	—
30-40	74	19	5	63	12
40-50	67	25	9	56	10
50-60	49	26	4	55	14
60-70	12	25	8	58	8

TABLE VII.
CHRONIC ARTHRITIS.

Percentage Incidence of Degrees of Gastric Acidity in Men and Women.

	Achlorhy- dria.	Hypochlor- hydria.	Normal Acidity.	Hyperchlor- hydria.
170 women	24	7	61	8
80 men	17	6	61	15

Younger subjects show abnormal acidity less often than older, and women more frequently have achlorhydria and less frequently hyperchlorhydria than men. This confirms the figures quoted by Bell (2), though apparently he is incorrect in the deduction from his own figures as to the relationship of achlorhydria to age. Bell quotes his figures as evidence against the accepted view that gastric acidity tends to decrease with age, whereas our analysis of the same figures gives the following result, showing that achlorhydria is more frequent in older subjects:

Analysis of Bell's Figures in Relation to Gastric Acidity and Age.

	Achlorhydria.	Hyperchlorhydria.
	%.	%.
187 patients younger than 40 years	11	22
238 patients older than 40 years	18	26

The difference between the frequency of hyperchlorhydria in young and old subjects is not so great in Bell's series as he emphasized. His error in deduction is apparently due to consideration of actual numbers and not percentages.

In view of the allowances which must be made for the effect of sex and age in gastric acidity, it is impossible to base on the figures given in Table V any definite deduction as to the relationship of gastric acidity to clinical types of chronic arthritis. The average age of the groups shows a progressive increase in the order in which they are placed (Table III). The average age being lower in patients in Groups A and B is partly explained by the shorter duration of the disease; the prolongation of the disease may be a factor in the reduction of gastric acidity.

Clinical signs of metabolic disorder are more frequent in Groups B and C, the latter more than the former, and Group C contains one of the highest percentages of achlorhydria; on the other hand, fibrositis is not a group in which metabolic defects are prominent, yet it shows the greatest divergence from the normal degree of gastric acidity.

A comparison of Table I with Table V shows general agreement between the results of this investigation and the records of previous writers. In detail there are discrepancies, some of which may be explained by the inadequate number of cases examined by previous observers, and by the employment by some of those observers of a method, i. e. the one-hour method, which is likely to increase the incidence of low acidity. The present investigation shows that reduced gastric acidity is not so frequent as is implied by a survey of current literature.

TABLE VIII.

Percentage Incidence of Different Rates of Emptying of the Stomach in Various Degrees of Gastric Acidity.

384 Examinations.		Hours.							Average No. of Hours.
		1	1½	2	2½	3	3½	4	
78	Achlorhydria	35	22	32	5	4	—	2	1.64
20	Hypochlorhydria	10	25	55	5	—	5	—	1.87
241	Normal	5	12	54	16	9	1	2	2.1
45	Hyperchlorhydria	9	9	58	20	4	—	—	2
									1.97

(384 examinations in 250 cases of arthritis and in 100 of other diseases, excluding Addison's anaemia and carcinoma of the stomach.)

Lower ranges of gastric acidity are associated with more rapid emptying of the stomach. The figures are in close agreement with those of other observers.

Analysis of Faecal Cultures.

Examination of aerobic faecal cultures obtained with the technique already described in a much larger number of patients with diseases other than are dealt with in this investigation, indicates that it is usual to find streptococci present on blood-agar plates, and that in approximately half of all specimens examined streptococci appear on culture in about equal numbers with coliform bacilli.

Although the intestinal flora in normal subjects have been shown to be inconstant (16), and the effects of diet and intestinal peristalsis are difficult to assess, it is useful to record the analysis of faecal cultures for the series under consideration.

Exact enumeration of colonies in routine examination of culture plates is impracticable, but approximation can be obtained by a considered estimate of relative proportions. This method is employed in obtaining the figures recorded in Table IX.

TABLE IX.

Percentage Incidence of Predominance of Streptococci and Coliform Bacilli in Cultures from Faeces.*

	No. of Cases.	Predominance of	
		Streptococci.	Coliform Bacilli.
		%.	%.
Chronic arthritis	250	31	25
Other diseases	75	23	28

* Predominance = 80 per cent., or more, of total colonies.

Results fall into one of three subdivisions: obvious predominance of (i) streptococci, (ii) coliform bacilli, (iii) an intermediate group where the incidence of streptococci and coliform bacilli is approximately equal. Table IX

indicates that in chronic arthritis predominance of streptococci is only slightly more frequent than that of coliform bacilli, while in other diseases in which intestinal toxæmia was suspected the predominance of streptococci is almost as great as in chronic arthritis.

Pure growths of coliform bacilli were obtained from 8 per cent. of the cases of arthritis, and from 13 per cent. of the cases of other diseases; in neither instance was the result associated with a distinctive type of gastric acidity. A pure growth of streptococci was obtained in only one case of arthritis and one case of other disease; and in both patients there was hyperchlorhydria with a normal rate of emptying of the stomach.

TABLE X.

Percentage Incidence of the Predominance of Streptococci and Coliform Bacilli in Cultures from Faeces in Patients with Different Degrees of Gastric Acidity.*

	250 Cases.	Streptococci predominant. %	Chronic Arthritis. Approximately equal In- cidence of Streptococci and Coliform Bacilli.	Coliform Bacilli predominant. %
			%.	
Achlorhydria and hypochlorhydria	72	40	49	11
Normal acidity	152	26	43	31
Hyperchlorhydria	26	35	38	27
	75 Cases.		Other Diseases.	
			%.	
Achlorhydria and hypochlorhydria	14	23	41	36
Normal acidity	50	20	56	24
Hyperchlorhydria	11	36	28	36

* Predominance = 80 per cent., or more, of total colonies.

The figures in Table X do not supply evidence on which to base a positive deduction. In chronic arthritis there is a relatively small percentage (11 per cent.) of hypochlorhydria in which streptococci are found in the faeces in only small numbers, i. e. one colony of streptococci to five of coliform bacilli. On the other hand, there is a marked predominance of streptococci in only 40 per cent. of cases of low acidity in contrast to a similar marked predominance of streptococci in 35 per cent. of hyperchlorhydria; the latter figure is approximately the same as in other diseases.

On the whole, streptococci are slightly more numerous in faecal cultures from cases with lower acidity, but the tendency is not particularly marked.

The majority of streptococci recovered from the faecal cultures are composed of three types of *Streptococcus faecalis*. Less frequently are isolated streptococci of a type such as normally inhabit the mouth and naso-pharynx which must be swallowed constantly in very large numbers, i. e. the many varieties of *Streptococcus viridans* and non-haemolytic strains which are not *Streptococcus faecalis*.

Were gastric hydrochloric acid the main factor in destruction of such

bacteria, the survival in the faeces of streptococci of the buccal type might have some relationship to free gastric acidity.

TABLE XI.

Presence of Streptococci of the Buccal Type, in Cultures from Faeces, in Relation to Gastric Acidity.

	Chronic Arthritis.		Other Diseases.	
	No. of Cases.	%.	No. of Cases.	%.
Achlorhydria and hypochlorhydria	72	20	14	50
Normal acidity	152	13	50	20
Hyperchlorhydria	26	11	11	36
Total	250	15	75	28

In only 15 per cent. of cases of arthritis are the buccal types of streptococci recovered, though more frequently if associated with lower than with higher gastric acidity. On the other hand, 28 per cent. of cultures in other diseases contain streptococci of the buccal type, i. e. almost twice as frequently as in chronic arthritis. The difference between the possible effect of achlorhydria and of hyperchlorhydria is small. This suggests that gastric HCl cannot be the main factor in the destruction of buccal micro-organisms. Other factors may be the action of the digestive secretions, apart from acid, and of katabolic substances produced in the course of digestion serving as selective media for different bacteria.

Urine Cultures.

Even in the absence of an infective lesion of the urinary tract, it is common practice to make cultures from urine passed under aseptic conditions with the object of isolating micro-organisms that may pass intermittently into the blood from a focus of infection and be excreted by the kidney. The hepatic barrier on the portal circulation is important in the arrest of bacteria and toxic products from the intestinal tract. In marked intestinal toxæmia it is reasonable to presume that there should be some hepatic inefficiency. The possibility of demonstrating this has been suggested by Rolleston (15). An investigation along these lines in chronic arthritis would be profitable, as intestinal toxæmia is so frequently considered to be present in this disease.

There is constant difficulty in interpretation of many cultures made from urine, due to the tendency of a few colonies of certain bacteria to develop, however strict may be the technique of obtaining the specimen. These bacteria, probably parasites on the mucous surface of the urethra, are mainly *Staphylococcus albus* and diphtheroid bacilli.

The significance of positive cultures depends to some extent on intensity of infection. In doubtful results repeated specimens are necessary. In an estimated half of positive cultures recorded in Table XII, the colonies have been considered negligible, i. e. less than ten colonies on a plate culture.

TABLE XII.

Cultures of Urine in 240 Cases of Chronic Arthritis.

63 % Negative.	37 % Positive.
Bacteria isolated in positive cultures.	
49 % Staphylococci (albus)	
19 % B. coli (includes 2 % atypical B. coli)	
18 % Streptococci (includes 10 % viridans	} Buccal,
1 % non-haemolytic	
7 % faecal)	
14 % Diphtheroid bacilli	

TABLE XIII.

CHRONIC ARTHRITIS.

Relationship of Gastric Acidity to Positive Urine Cultures.

	% of Cases of		
	Achlorhydria and Hypochlorhydria.	Normal Acidity.	Hyperchlorhydria.
Various micro-organisms	35	38	28
Streptococci	5	7	12

Streptococci of the buccal type are found in urine more frequently than the faecal type (Table XII). Possibly this is due to the frequency of focal sepsis in the buccal cavity and pharynx.

There is an insignificant difference in the incidence of positive cultures between three degrees of gastric acidity; streptococci have been found in urine in cases with hyperchlorhydria more frequently than in those with lower ranges of acidity (Table XIII).

The preponderance of staphylococci among positive cultures must be discounted to some extent because of the prevalence of these organisms on the mucous membranes, and the difficulty in devising a reliable technique.

Summary.

1. The incidence of achlorhydria and hypochlorhydria in chronic arthritis is five times as great as in normal subjects, but only slightly greater than in other diseases.

2. Hyperchlorhydria in chronic arthritis has the same incidence as in normal subjects, being about a third as frequent as in other diseases.

3. Chronic arthritis associated with sepsis (Group B) is accompanied by a range of gastric acidity less divergent from normal than other groups.

4. Chronic arthritis not definitely associated with sepsis (Group C) is more often accompanied by achlorhydria. This group shows more signs of metabolic disorder.

5. Non-articular fibrositis diverges still more from normal by a higher incidence both of achlorhydria and hyperchlorhydria.

6. Osteo-arthritis is accompanied by an incidence of achlorhydria nearer to normal, but the percentage of hyperchlorhydria is high.

7. Streptococci have been isolated in 92 per cent. of faecal cultures from 250 cases of chronic arthritis and from 87 per cent. of seventy-five cases of other diseases.

8. Marked preponderance of streptococci (80 per cent. of total colonies) in faecal cultures in chronic arthritis is only slightly more frequent than in other disorders possibly associated with intestinal toxæmia. Marked preponderance of coliform bacilli occurs almost as frequently as that of streptococci.

9. Streptococci are rather more predominant in faecal cultures in cases of chronic arthritis with low than with high grades of gastric acidity.

10. Streptococci of the buccal types have been recovered from the cultures of faeces in 15 per cent. of the cases of chronic arthritis and 28 per cent. of other diseases.

11. 37 per cent. of cultures from urine are positive in cases of chronic arthritis, but these bear no relationship to gastric acidity.

12. Streptococci have been isolated from the urine in cases of hyperchlorhydria more frequently than in cases of hypochlorhydria and achlorhydria, in the ratio of twelve and five.

Conclusions.

The association of achlorhydria and hypochlorhydria with chronic arthritis is not so marked as to justify the conclusion that it is a primary factor in the aetiology of the disease. In general, the frequency of abnormal gastric acidity approaches that found in a wide group of other diseases; it may be the result of depression of function due to debility and asthenia. There is evidence that achlorhydria in chronic arthritis allows more ready multiplication in the bowel of streptococci, and may be therefore an accessory factor in the aetiology of the disease.

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THE EFFECT OF MINERAL ACID ON ACID-BASE REGULATION IN HEALTH AND IN NEPHRITIS¹

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Introduction.

OUR growing knowledge of the variations of the acid-base balance in the blood and the demonstration that substances which disturb this balance are potent therapeutic agents have combined to renew our interest in the mechanism by which this balance is preserved. Whereas sudden disturbances are swiftly compensated by changes of respiration, the permanent readjustment depends upon the kidneys, and the capacity to perform this duty is one of the most important of their functions.

The customary diet of man provides an excess of acid radicals for elimination. This excess of acid is derived partly from the ash, which is itself acid except in vegetarian diets, and partly from non-volatile organic acids formed in the processes of metabolism; such organic acids are eliminated in the urine in amounts equivalent to half a litre or more of decinormal acid a day. Additional calls on the power of acid excretion may be made by the physician, for it is usual to give hydrochloric acid in moderately large amounts (500 c.c. 0.1 N per day) in the treatment of Addison's anaemia and some forms of dyspepsia, and the treatment of oedema by acid-producing salts such as ammonium chloride is not infrequent. The observations recorded here show the manner and effectiveness of the response which the kidney makes to such demands in normal and impaired states of renal function.

Henderson and Palmer (1) have described in detail the mechanism of acid excretion. The excretion of urine more acid than the blood enables a small amount of surplus acid to be eliminated; this fraction can be estimated by titrating the urine back to the reaction of the blood, pH 7.4, and it is called the titratable acidity. The effectiveness of this process in saving base is definitely limited and can only affect the base bound by phosphoric, carbonic, and the organic acids. At the lowest pH that the kidneys can attain, pH 4.7, the sulphates and chlorides must be accompanied into the urine by their full complement of base,

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since the existence of these acids in the free state at this pH is possible only in minute amount; economy of the bases bound by these strong acids is therefore impossible. Phosphoric acid binds 1.8 equivalents of base at the pH of the blood and 1.0 equivalent at the minimum urinary pH; a saving of 0.8 equivalent of base can therefore be effected by excretion of urine at the most acid reaction. The difference in the base bound by phosphate at the usual reaction of about pH 6 and at the minimum pH of 4.7 is very small. Haldane, Hill, and Luck (2) have shown that the phosphate excretion is itself increased when an artificial acidosis is produced; such extra phosphate will carry at least 1.0 equivalent of base into the urine and will provide at most 0.8 equivalent for combating the acidosis. A similar saving may be effected on the base bound by organic acids.

In its ability to excrete acid in combination with ammonia the kidney possesses a more effective mechanism for the economy of fixed base. The ammonia excretion in the ketosis of severe diabetes demonstrates the great expansion of which this process is capable.

Any acid which is not dealt with in one of these ways must be excreted in combination with fixed base. Of this the body possesses considerable reserves. A levy is made on base reserves of the blood and tissues, which, by a proportionate reduction of their water content, can present a part of their salts for excretion without disturbing the general osmotic pressure of the body fluids (Gamble, Ross, and Tisdall (3)). The bones form a vast reserve of base, but the solution of calcium phosphate and calcium carbonate takes place so slowly that the effectiveness of this process in meeting an emergency is small. Lastly, there is a diversion of calcium and magnesium from the stools to the urine which has been found to occur when mineral acid is given (4).

Henderson and Palmer (5) and Van Slyke, Linder, &c. (6), have shown that in chronic glomerulo-nephritis there is a diminished excretion of ammonia and an increase in the urine volume and acidity; the failure to excrete ammonia becomes greater as renal function fails and nitrogen retention increases. In acute nephritis reduction in ammonia excretion is sometimes found. This failure of the kidneys to excrete ammonia is probably the main cause of the acidosis of advanced nephritis. Nash and Benedict (7) have brought forward experimental evidence to show that the ammonia of the urine is formed in the kidneys, presumably from urea, and that it is not carried to them by the blood-stream, as was so long supposed. This hypothesis was supported by the work of Loeb, Atchley, and Benedict (8), and of Rabinowitch (9), and by the findings of Russel (10) and of Van Slyke, Linder, &c. (6), that the fall of urinary ammonia in nephritis is not accompanied by an accumulation of ammonia in the blood. Bliss, however, found that ammonia is formed in other organs as well as the kidneys, particularly in the spleen and pancreas, and that the ammonia which is lacking in the urine in nephritis can be found in the vomit; if vomiting was absent an increase of ammonia could be demonstrated in the blood (11). Benedict and Nash (12) believe that the ammonia found by Bliss in the vomit

and in the pancreatico-duodenal and splenic veins was of intestinal origin, and maintain that all the ammonia of the urine is formed in the kidneys.

It was hoped by giving acid to persons with different varieties of nephritis to demonstrate these changes in cases in which they were not naturally apparent and to show what further adjustments would become available. As test substance dilute hydrochloric acid was chosen. By using ammonium or calcium chloride a severer test could have been applied, but giving an ammonium salt would have obscured the results, since the excretion of ammonia was one of the points to be determined, and the details of the absorption of the calcium salt are unknown.

Methods and Material.

At least three days before the observations were started the subjects were placed upon a constant diet, which in most of the periods was salt poor. No special diet kitchen was available, but every effort was made to make the variation in diet from day to day as small as possible and to ensure that no change in the salt intake occurred during the period of observation. The intake of fluid was constant at 1,500 c.c. Medication was suspended. After a control period of two or three days acid was given in amounts corresponding to 500 to 1,000 c.c. 0.1 N solution a day. Most of the subjects had little difficulty in taking the full amount when it was divided into three doses and given with plenty of water, taken of course from the daily allowance of fluid. The acid was given in this way for two to four days, and in some of the subjects the observations were continued for one or two days afterwards.

The analyses were made on twenty-four-hour specimens of urine which had been mixed with toluol and kept in a cool place from the time of obtaining the individual specimens. Determinations were made of pH (Henderson and Palmer (13)), titratable acidity (Henderson (1)), ammonia (Van Slyke and Cullen (14)), chloride (Volhard), sulphate (Rosenheim and Drummond (15)), phosphate (uranium titration), organic acid (Van Slyke and Palmer (16)), total nitrogen (Kjeldahl), and creatinin. In some of the earlier observations the fixed base was estimated by subtracting the sum of the ammonia and titratable acid from the equivalent of the total acids; in most cases the base was determined directly by the methods of Fiske (17) or Stadie and Ross (18). The base appearing in the urine with bicarbonate was not separately determined, but may be estimated from the pH (Gamble (19)); except in the urines of high pH the amount is negligible.

Venous blood was taken before the acid was given and on the last day of the acid period. A minimum of stasis was used and the blood was taken at the same hour on each occasion. The serum was separated as soon as possible and determinations made of pH (Hastings and Sendroy (20)), CO_2 (Van Slyke and Neill (21)), chloride (Van Slyke (22)), inorganic phosphate (Benedict and Theis (23)), and total fixed base (Fiske (17) or Stadie and Ross (18)). The bicarbonate was calculated, 6.11 being taken as the pH of serum.

TABLE I.

Case.	Day.	Acid given c.c. 0.1 N.	Vol. c.c.	pH.	Base bound by				Titratable Acid.	Ammonia.	Fixed Base.	Creatinine gm./day.	Total N ₂ . gm./day.
					Cl.	SO ₄ .	PO ₄ .	Organic Acids.					
I. Normal	1	—	1500	5.0	270	720	176	—	290	654	616	1.1	12.0
	2	—	1590	5.3	222	572	205	—	262	698	654	1.2	15.5
	3	—	1800	5.1	197	1370	336	—	433	1090	973	1.2	12.4
	4	1000	1500	4.9	558	1227	315	—	374	1140	1307	1.0	9.8
	5	1000	1500	5.1	994	1128	224	—	305	1172	1306	1.4	18.1
	6	1000	1640	5.4	990	1415	285	—	335	1689	1106	1.4	12.0
	7	—	1520	5.4	940	1180	265	—	275	1520	957	1.4	11.5
	8	—	720	5.5	782	563	215	—	223	1184	439	1.3	—
II. Normal	1	—	1110	5.8	935	960	316	480	305	551	1835*	—	9.6
	2	—	1220	5.8	1340	755	352	440	310	419	2158*	—	11.1
	3	—	1620	5.8	1533	496	358	414	292	376	2153*	—	10.5
	4	1000	1380	6.0	1605	869	466	600	276	850	2412*	—	12.9
	5	1000	1450	5.1	1853	1245	390	386	483	777	2614*	—	8.5
	6	1000	1400	6.3	1440	868	356	330	70	1253	1641*	—	8.8
	7	—	720	5.7	1100	533	288	350	281	784	1191*	—	—
III. Normal	1	—	1350	5.6	1800	770	575	—	568	412	—	—	16.3
	2	—	860	5.7	1250	620	288	—	344	402	—	—	13.6
	3	—	1300	5.6	1250	740	480	—	510	452	—	—	16.6
	4	500	1670	5.2	2320	620	425	—	506	538	—	—	13.9
	5	600	1000	5.2	1780	580	350	—	470	590	—	—	13.2
	6	1000	1800	5.0	2430	617	370	—	513	760	—	—	14.4
IV. Normal	1	—	1200	5.9	116	650	320	—	176	623	364	1.2	10.4
	2	—	1320	5.9	125	670	290	—	179	808	214	1.3	9.8
	3	—	1280	5.8	107	666	315	—	182	690	304	1.2	10.3
	4	1000	1500	5.6	576	721	401	—	254	690	755	1.4	11.0
	5	1000	1540	5.5	921	696	380	—	283	943	764	1.2	10.2
	6	1000	1460	5.5	1111	590	370	—	325	1308	656	1.3	10.6
	7	1000	1600	5.4	946	671	398	—	305	1165	724	1.2	11.1

V. Mild chronic nephritis	1	—	1830	5-8	1280	1108	214	700	375	540	2387*	1-2	7-5
	2	—	1680	5-8	1170	1300	168	525	314	638	2211*	1-0	8-3
	3	1000	1960	5-3	1510	1153	141	420	323	545	2356*	0-9	8-1
	4	1000	1830	5-1	1575	1330	167	520	381	636	2355*	1-2	7-5
	5	1000	1825	5-4	1435	1285	188	520	456	769	2200*	0-9	7-4
	6	1000	1775	5-4	1235	1222	201	245	462	904	1540*	1-05	8-1
	7	—	1750	5-3	1380	1280	242	500	498	1070	1834*	1-1	9-2
VI. Chronic hydraemic nephritis	1	—	1125	5-9	210	166	52	—	162	310	214	1-5	—
	2	—	1580	5-9	170	158	46	—	142	321	204	1-4	—
	3	1000	1525	5-8	208	194	168	—	198	429	229	1-5	—
	4	1000	1600	5-6	356	218	146	—	224	507	248	1-6	—
	5	1000	1710	5-6	605	209	154	—	256	610	274	1-4	—
	6	1000	1825	5-5	730	186	190	—	245	650	274	1-5	—
	7	—	1315	5-6	700	—	—	—	237	684	230	—	—
VII. Subacute hydraemic nephritis	1	—	1730	7-0	192	910	327	—	35	1455	—	—	11-9
	2	—	1450	7-5	123	582	291	—	0	1390	—	—	11-3
	3	—	1560	7-5	160	615	326	—	0	1254	—	—	9-9
	4	500	2230	6-9	152	624	334	—	134	1075	—	—	10-5
	5	750	2250	7-5	327	918	312	—	0	1897	—	—	11-0
	6	850	2475	6-7	622	958	296	—	250	1719	—	—	12-4
	7	—	—	—	—	—	—	—	—	—	—	—	—
VIII. Chronic interstitial nephritis	1	—	1180	5-3	255	319	186	—	245	472	450	1-0	—
	2	—	1250	5-6	237	285	140	—	173	455	416	1-0	—
	3	—	1450	5-8	—	302	160	—	207	465	—	1-0	—
	4	1000	1420	5-4	283	278	142	—	187	437	435	1-0	—
	5	1000	1250	5-7	521	265	144	—	125	472	640	0-8	—
	6	1000	1710	5-1	863	323	166	—	250	563	934	1-0	—
	7	1000	1550	5-2	1162	257	172	—	201	539	1170	0-9	—
	8	—	1210	6-0	664	270	160	—	156	686	522	—	—
IX. Chronic azotaemic nephritis	1	—	960	7-2	263	770	150	700	19	726	745*	—	6-1
	2	500	1670	7-0	636	958	161	555	33	970	1003*	—	7-1
	3	500	1670	7-0	800	855	235	380	108	757	865*	—	7-9
X. Chronic azotaemic nephritis	1	—	1150	5-0	307	262	188	—	242	108	603	0-8	5-6
	2	—	1210	5-0	354	257	188	—	266	137	596	0-7	—
	3	1000	1790	4-9	505	398	182	—	284	105	1106	—	6-9
	4	1000	1620	4-7	723	532	184	—	326	123	1455	—	7-3
	5	—	1480	4-9	613	531	140	—	258	113	1275	—	5-9

* Fixed base not directly determined.

The observations reported were made upon four normal individuals, Cases I to IV; one patient recovering from an exacerbation of a very mild chronic nephritis, Case V; two suffering from nephritis of the pure hydraemic type (nephrosis), Cases VI and VII, of whom the former was free from oedema at the time; and three patients with definite renal insufficiency and high blood-pressure, Case VIII having chronic interstitial nephritis (nephrosclerosis) and Cases IX and X chronic nephritis.

Results and Discussion.

The results of the urine analyses are given in Table I. On examination, more especially of the figures for ammonia and fixed base, it will be apparent that the results fall into three groups which correspond to the normal persons, the hydraemic patients, and the azotaemic ones. An example of each kind of result is illustrated in Charts I, II, and III. These charts show the daily variation of some of the urinary constituents above and below the average for the days of the control period, which average is represented by the zero line; the substances charted are the chloride, ammonia, titratable acidity, and fixed base. All substances are recorded as their equivalent in c.c. of decinormal acid or base.

It is apparent that in all cases the extra chloride excreted in the urine was considerably less than the amount of chlorine in the acid given; this may have been due to incomplete absorption, excretion into the bowel, and possibly to a retention of a small part of it in the tissues as sodium chloride.

The effect of the fall in pH and increased excretion of phosphate was small, as was shown by the comparatively small change in the titratable acidity; on one day only was the increase more than 200 c.c. of 0.1 N solution (Case VII), and the usual increase was 100 c.c. or less. In general there was no difference between the groups in regard to the pH and titratable acidity. The pH varied from six to five. In one case of severe glomerulo-nephritis and one of hydraemic nephritis the initial specimens of urine were neutral and the titratable acidity very small. The pH fell slightly and the titratable acidity increased in both when the acid was given. In both the ammonia output to begin with was high, and in both the urine was sterile. This is an unusual state of affairs in advanced nephritis, but we have observed it in one other case, in which, however, no cultures of the urine were made (6).

Normal group. The response of the first group, which contains four normal persons and Case V with a very mild chronic nephritis, showed the following characteristics. An extra excretion of fixed base occurred promptly after the acid was given, and sometimes it preceded any increase of ammonia. In Cases I and IV this extra base excretion continued throughout the time that the acid was given, but in Case II it was present for the first two days only and was followed by a fall below the figure for the control period. It appears probable that there

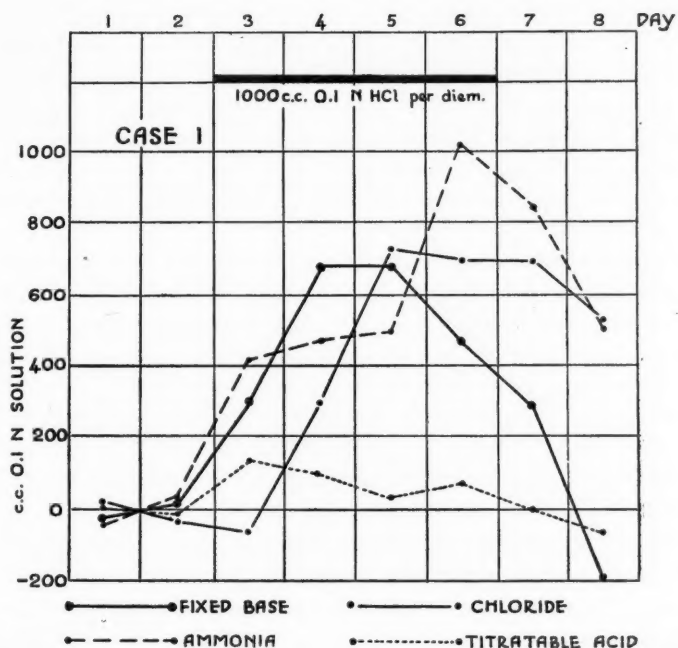


CHART I. *Case I*, normal person. The zero line represents the average daily values for the preliminary period, namely chloride 245 c.c., ammonia 676 c.c., titratable acid 276 c.c., and fixed base 635 c.c.

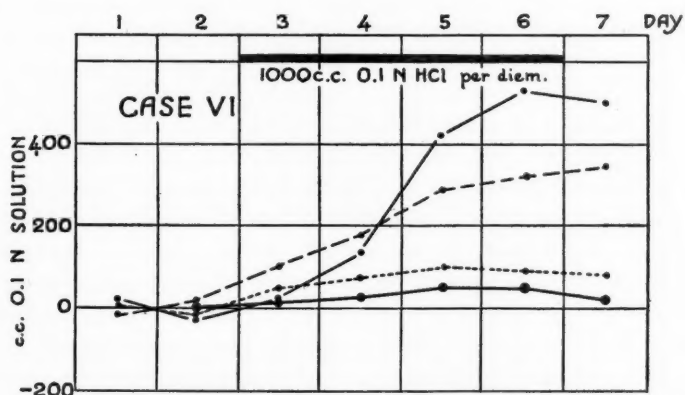


CHART II. *Case VI*, hydraemic nephritis. Zero represents—chloride 190 c.c., ammonia 315 c.c., titratable acid 152 c.c., and fixed base 209 c.c.

is a store of readily mobilizable fixed base with which the body easily parts, and that this store varies considerably in size from person to person. The ammonia output tended to rise more slowly, and in Cases IV and V no rise was apparent till the second day. The highest ammonia figures were obtained either on the last day of the acid period or on the first day following this. The extra ammonia amounted to from 400 to 1,200 c.c. The normal kidney can readily deal with the amount of acid given; the amount of ammonia and acid eliminated in diabetes and in calcium or ammonium chloride therapy have exceeded the amounts recorded here three- or fourfold.

Hydraemic group. The results depicted in Chart II were obtained in the case of a patient suffering from hydraemic nephritis without increase of blood-pressure—chronic nephrosis (Case VI). Oedema was absent at the time of observation. The chloride and ammonia output increased in a satisfactory manner, but the fixed base, which was low in the control period, did not increase more than 50 c.c. The departure from the normal consisted in a failure to mobilize and eliminate fixed base. No other disability was demonstrated. Case VII, the remaining patient in this group, was in a similar but rather more acute condition; oedema was present. The study was incomplete. Less acid was given and the indirect method for the determination of base failed, the great amount of protein making the titration of organic acids impossible. The level of ammonia excretion was high throughout and the reaction of the urine only slightly acid or alkaline (pH 6.7 to 7.5). Cultures showed the urine to be sterile. During the test period the ammonia output increased greatly. There appears, therefore, to be no impairment of ammonia formation in this condition, but the normal increase in fixed base excretion may fail to occur. This is a fresh demonstration of the difficulty these patients have in regulating the interchange of salts and water between the tissues and the blood, and it also supports the prevailing opinion that this difficulty is primarily in handling the basic ions. When oedema is present large amounts of acid may cause a copious diuresis of salts and water to occur; calcium or ammonium chloride have usually been employed for this purpose (Blum (24), Keith (25), and Gamble (26), and their collaborators). The explanation which is given for this phenomenon is that a fall of pH occurs in the blood and tissues, setting free base held by the various tissue proteins; this base with a corresponding quantity of water returns to the blood, where the kidneys are able to deal with them (Haldane, Hill, and Luck, 2). It is possible that the power of producing ammonia has to be severely taxed before a diuresis results, and that the less ammonia the kidney is able to form the greater will be the chance of causing such a diuresis.

Azotaemic group. Charts III and IV show the changes which occurred in the third group. All the patients giving this type of response had moderate or severe renal insufficiency. Case VIII, the data of whom are illustrated in Chart III, was a patient with chronic interstitial nephritis with retinitis, a blood-pressure of 260/140, and a blood-urea of 72 mg. per cent. Chart III shows that although the initial level of ammonia output was high (463 c.c.), yet there

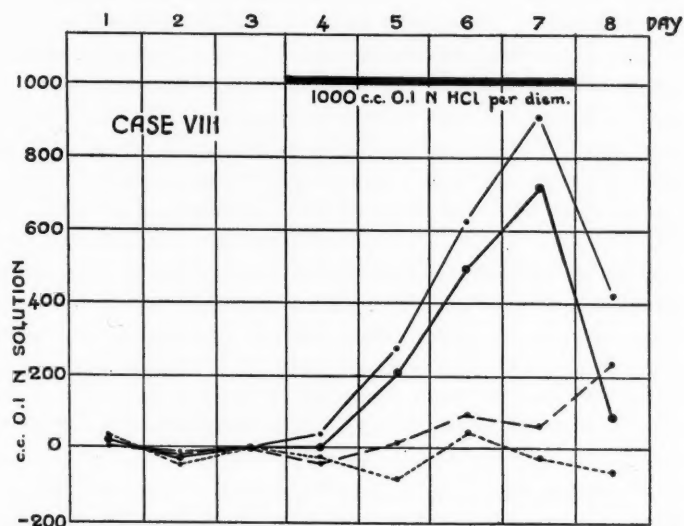


CHART III. *Case VIII*, chronic interstitial nephritis with moderate impairment of renal function. Zero represents—chloride 246 c.c., ammonia 463 c.c., titratable acid 209 c.c., and fixed base 433 c.c.

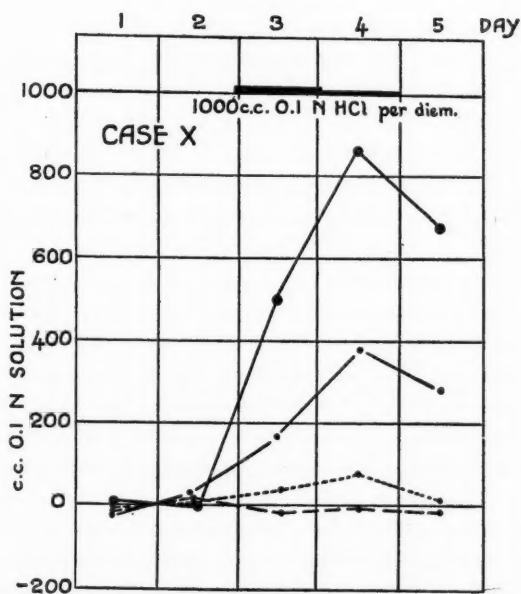


CHART IV. *Case X*, chronic azotaemic nephritis with advanced renal insufficiency. Zero represents—chloride 331 c.c., ammonia 123 c.c., titratable acid 254 c.c., and fixed base 600 c.c.

was very little reserve power of ammonia formation, the greatest increase being 200 c.c. on the last day. The bulk of the acid was excreted in combination with fixed base, and, since the patient was not oedematous, this extra base must have come from the blood or tissues. The pH of the urine decreased to 5.1, but the effect on the titratable acidity was negligible. Chart IV was obtained from Case X, a woman in the last stages of glomerulo-nephritis who died in uraemia two months later; in this instance the acid caused severe vomiting on the second day, so it was necessary to curtail the observation. The results are still more striking. The output of ammonia, which was small to begin with (123 c.c.), did not increase at all, but the output of fixed base increased very greatly and exceeded the extra output of chloride. There was also a great increase in the excretion of sulphate. No oedema was present. In Case IX the results were not so clear. The high level of ammonia excretion is unusual in a case of such severity and has already been commented upon. The small amount of acid given elicited a moderate increase of ammonia (200 c.c.) and a similar increase of fixed base. No symptoms were produced, but examination of the blood showed such a severe acidosis that the acid was discontinued.

Source of the extra base. The three patients in the third group showed a more or less complete incapacity to excrete the acid in combination with ammonia, and to compensate for this there was a much greater tax upon the base reserves of the blood and tissues than occurred in the normal persons. This was particularly evident in Case X (Chart IV). This patient was quite unable to increase her output of ammonia; the extra base on the second day amounted to over 800 c.c., and on the day following, when the acid had been discontinued, to 650 c.c. The opportunity was taken to make an investigation into the source of all this extra base, following the plan of Gamble, Ross, and Tisdall (3) in their study of the fixed base excreted during fasting. The urines were ashed by the Stolte method (27) and the ash analysed by the Tisdall and Kramer methods (28) for calcium, sodium, and magnesium; from the difference between the sum of these and the total fixed base the potassium excretion was calculated. For comparison similar figures were obtained for a normal person, Case I. Gamble, Ross, and Tisdall have presented a very complete analysis of the factors concerned in the metabolism of fixed base during fasting. They found that the base required to effect the excretion of the great quantity of organic acids produced during starvation was provided by a reduction in the volume of the body fluids, and not by a decrease in the concentration of base in the body; that this was so was shown by the practically stationary concentration of inorganic radicals in the plasma, and therefore in the tissue fluids, since these are in osmotic equilibrium with the plasma. This was so in our patient, but in the normal person a definite decrease in the concentration of base in the serum was observed. (See Table III.)

Since the concentration of potassium in extra-cellular water, as represented by the serum, is small in comparison with that of sodium, no great error is made if in the estimation of the source of the fixed base the potassium be assumed to be wholly derived from the intracellular fluids. The concentration of potassium

in muscle water is given by Katz (29) as 108 millimoles (mM.) per litre; if this figure is taken to represent the concentration of potassium in the other cells of the body, the volume of cell water consumed is readily calculated. The sodium contained in this amount of cell water, 46 millimoles per litre, is subtracted from the total sodium, and the remainder is that derived from extra-cellular fluids. Assuming that serum is representative of these and contains 135 millimoles per litre we can obtain the volume of extra-cellular water used. The results are extremely rough approximations.

Table II gives the results of our calculations, from which it is evident that the whole of the extra base excreted by the patient with uraemia was derived from cell water. The normal person was able to spare extra-cellular water in approximately equal amounts for the first three days. On the first day no loss of cell water could be detected, but on the second and third it appeared in increasing amounts and exceeded the loss of extra-cellular water. On the fourth day of the acid period the loss from both sources fell to low figures and the excretion of ammonia reached its maximum. This method was applied by Gamble, Blackfan, and Hamilton (26) to normal children and to children with nephritis and oedema. The normal child showed losses from cells and extra-cellular fluids of approximately equal size, and this was the case in our normal subject; calculations from the figures given by Stehle and McCarty (30) for two normal adults who took acid in doses such as we gave show a considerable preponderance of water lost from the cells. Gamble's child with oedema lost an excess of extra-cellular water, as might be expected.

The calcium and magnesium excretion formed a much greater proportion of the total base excretion in Case I than in Case X. The maximum increase on the original figure was the same in both,—114 per cent. They maintained the same proportion of the total base excretion throughout the observations on Case X, and slightly increased their proportion in Case I.

It appears, therefore, that normal persons have base and water which can be readily spared both from the extra-cellular fluids and from the cells themselves. When this reserve is exhausted the ammonia mechanism takes charge of the situation, and, as is shown in Case II, base may actually be replaced in the tissues while acid is yet being given. On the other hand, in severe renal insufficiency a much larger quantity of base is required, and practically none can be spared from the extra-cellular fluids; these may already show considerable abnormalities due to the drain on their resources in the maintenance of life under daily conditions. The brunt of the attack therefore falls on the cell fluids, and the depletion of these was probably the cause of the vomiting which occurred in Case X.

Sulphate. The excretion of sulphate rose in some of the normal and some of the nephritic subjects while the acid was being given. In others no such rise took place. The rise was probably related to protein metabolism, but no evidence of a sufficient increase in protein metabolism was evident from the nitrogen excretion. Over such a short period this may not exclude this explanation.

TABLE II.

Case Diagnosis.	Day.	Acid given.	Total Base.	Ca.	Mg.	Na.	K.	Muscle Water containing Extra K. c.c.	Extra Na in Muscle Water.	Total Extra Na.	Na derived from Extra- cellular Water.	Extra-cellular Water. c.c.
I. Normal	1	—	616	188	135	44	287	—	—	136	136	100
	2	—	654	318	310	180	165	—	—	193	127	95
	3	1000	973	383	244	237	443	144	66	255	164	120
	4	1000	1307	293	214	299	500	197	91	54	42	31
	5	1000	1306	412	281	98	315	26	12	15	15	11
	6	1000	1106	418	255	59	225	—	—	—	—	—
	7	—	957	—	—	—	—	—	—	—	—	—
	8	—	439	—	—	—	—	—	—	—	—	—
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X. Chronic azotaemic nephritis	1	—	603	33	63	333	174	—	—	—	—	—
	2	—	596	—	—	—	—	—	—	—	—	—
	3	1000	1106	53	102	428	523	323	148	95	—	—
	4	1000	1455	66	138	560	691	478	219	227	8	8
	5	—	1275	67	123	510	575	371	170	177	7	7
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The bases are expressed by their equivalent in c.c. of 0.1 M solution of a monovalent base.

Muscle water was assumed to contain 108 mM. K and 46 mM. Na per litre, and serum to contain 135 mM. Na.

Water. A slight increase in the output of water occurred in the normal persons when the acid was being given. There was no change in Case V. In the other cases of chronic nephritis, both of hydraemic and azotaemic types, there occurred a quite definite moderate diuresis. The source of this water in the azotaemic patients is to be attributed to the changes in base content of the body which have been described above. In Case VI the extra water output was not very great, but as no extra base was excreted the same explanation will not hold. The serum analyses showed that a definite concentration had occurred in the inorganic ions at the end of the acid period; this concentration points to a loss of water and indicates a probable source for the extra water excreted.

TABLE III.

Case.	Diagnosis.	pH.	Base bound by				Total Base.
			HCO ₃ .	Cl.	PO ₄ .	Protein and Organic Acid.	
			mM.	mM.	mM.	mM.	mM.
I	Normal	7.46	28.7	99.2	2.6	29	159
		7.28	22.3	104	2.6	24	153
II	Normal	7.34	30.8	100	2.8	17	150
		7.30	24.8	108	2.8		
III	Normal	7.32	28.9	100	2.1		
		7.30	27.1	104	2.3		
IV	Normal	7.33	30	98	2.3	24	154
		7.32	26	102	2.3	20	150
V	Mild chronic nephritis	7.34	27.5	100	3.2		
		7.22	20	111	3.1		
VI	Hydraemic nephritis	7.25	27.6	99	2.9	6	135
		7.18	20.5	113	3.1	9	145
VIII	Chronic interstitial nephritis	? 7.17	25.2	95	3.6	33	157
		7.19	17.6	106	3.4	27	154
VIII a	Chronic interstitial nephritis	7.25	29.9	96	3	33	162
		7.24	25.7	103	2.6	27	158
IX	Chronic azotaemic nephritis	7.17	17.2	113	4.2	23	157
		7.10	11.8	115	4.8	21	153
X	Chronic azotaemic nephritis	7.25	19.4	102	5.4	31	158
		7.17	13.05	104	5.3	36.7	159

Changes in the Acid-base Balance of the Serum. It has been shown by Peters, Bulger, Eisenman, and Lee (31) that in different physiological and pathological states no one of the inorganic constituents of the serum is maintained rigidly constant at the expense of the others, but that the changes tend to the restoration of a normal equilibrium. In healthy individuals the protein, bicarbonate, and chloride reciprocate in their changes and assist in maintaining the total acid and total base at a constant level.

In the present observations it was found that the acid produced definite changes in the chloride, bicarbonate, pH, and base of the serum in the normal people, and that these changes were exaggerated in nephritis. The base varied the least, but a fall equivalent to 4 millimoles (mM.) of monovalent base occurred

fairly regularly. In the controls the chlorides increased 4 to 8 mM.; part of this increase was at the expense of the bicarbonate, so that the sum of the chloride and bicarbonate remained comparatively constant. Since the reaction shifted towards the acid side the base binding power of the serum proteins must have been less, and a small amount of base set free to carry chlorine. In these cases the pH at the close of the acid period was close to 7.30.

In Case V, the patient recovering from an exacerbation of a very mild chronic nephritis, the serum showed a greater fall in pH and bicarbonate and a greater increase in chloride. There was therefore evidence of persisting impairment in power to hold the acid-base balance within the normal limits.

In Case VI, hydraemic nephritis, the chloride increased 14 mM. and the bicarbonate decreased by 7, so that the sum of chloride and bicarbonate varied more than usual. The base increased from the remarkably low figure of 135 mM. to 145 mM.; this has already been noted and adduced as evidence of an increase in the concentration of the serum. From these observations, and from experience of similar cases, the impression was formed that the disorder of inorganic metabolism is apt to be particularly severe and widespread, and that there is an especial liability to the early and spontaneous development of acidosis. Usually this acidosis is mild, and possibly it is of benefit by encouraging the shift of water from the tissues to the blood. Of itself, therefore, it may not need correction; indeed excellent results may sometimes be obtained by giving acid-producing salts, such as ammonium chloride. Occasionally this early acidosis is more severe, and untoward symptoms occur, even general convulsions; but since it may occur relatively early in the course of the disease and without any great retention of non-protein nitrogen, it is distinct from the acidosis of true uraemia. Correction of the acidosis with sodium bicarbonate or alkaline sodium phosphate may be followed by relief of symptoms and a striking recovery of renal function.

In chronic interstitial nephritis the changes were somewhat greater than in the controls, and the acid-base balance shifted more to the acid side.

In both the advanced cases of glomerulo-nephritis there was a moderately severe acidosis before the acid was given. Case IX was in a better state than Case X, and she is still alive, eighteen months after these observations were made. In her case the initial acidosis was severe, and although a much reduced dose of acid was given, a very severe state of acidosis was produced, which was quite without symptoms at the time; vomiting occurred next day, however. The chloride was already high, and increased by 2 mM., while fixed base decreased by 4 mM. It is plain that the reduction in bicarbonate was not accounted for by the increase in chloride, but depended also on other factors, of which the reduction of base was probably the most important. Case X was similar in that the decrease in bicarbonate greatly exceeded the rise in chloride, but in this instance the base was not decreased. Since the base bound by the plasma proteins would be decreased by the fall in pH, the other undetermined acids must have increased by at least 6 mM. Before the acid was given, the sum of the undetermined acids, allowing 10 mM. for the proteins, exceeded the normal limit, which is given

by Peters as 20 mM. (31). This state was made worse by the acid, and it appears that an increase of the undetermined acids, such as occurs in uraemia (Marrack (32), and Bulger, Peters, et al. (33)), was provoked by it in this patient. The above authors noted that the serum base shows a tendency to fall in severe cases of nephritis, and they attribute nephritic acidosis to this and to the accumulation of undetermined acids; they also report low chlorides, which we did not find, but this may have been because our patients were selected for their freedom from vomiting.

Summary and Conclusions.

Dilute hydrochloric acid, in amounts corresponding to 500 to 1,000 c.c. decinormal acid a day, was given to four normal persons and to six patients with nephritis for periods of two to four days. The changes in the blood and urine were studied with the object of demonstrating the mechanisms available for maintaining the normal state and the effect on them of renal disease.

In the control cases a quantity of fixed base was available for excretion with the acid. This store was exhausted in two or three days, and its place was taken by ammonia, which was excreted in increasing amounts. The extra base was derived from cellular and extra-cellular water.

In one mild case of chronic nephritis similar results were obtained.

The patients with chronic hydraemic nephritis without gross oedema showed an adequate response in ammonia formation, but the extra excretion of fixed base was lacking.

The azotaemic patients showed diminished power to form extra ammonia. This defect became greater as renal function failed. In compensation there was a much greater excretion of fixed base, which in one case was derived entirely from cellular water.

The changes in the sera consisted of increases in the chloride and decreases in bicarbonate and pH. The total base usually decreased slightly. In the patients these changes were more extensive, giving evidence of failure to adjust the acid-base balance with the customary delicacy. In the two patients whose renal function was greatly impaired severe acidosis was produced.

It is a pleasure to record my gratitude to Professor F. R. Fraser for facilities he has given me for doing this work, and to the Medical Research Council for a personal grant. My thanks are also due to the Ward Sisters of the Medical Unit for their help in the essential task of supervising the patients.

Case Records.

Case I. Male, aged 42 years. In hospital for spastic paraplegia due to proliferative gliosis. Apex beat in fifth space $3\frac{1}{4}$ in. from mid-line. Blood-pressure 138/90. Urine normal chemically and microscopically. A salt-free diet was given for three days before the control observations were started.

Case II. Male, aged 33 years. Convalescent from encephalitis lethargica. Apex beat in fourth space in nipple line. Blood-pressure 130/75. Urine normal. A salt-free diet was not given to this subject; no added salt was allowed.

Case III. Male, aged 33 years. Not in hospital. The first series of observations were made on this subject; the diet was not salt free and could not be so strictly controlled as in the others.

Case IV. Male, aged 22 years. Spondylitis deformans. Apex beat in fifth space, four inches from mid-line and of normal force. Blood-pressure 135/80. Urine normal. Urea concentration in urine after urea feeding 3.6 per cent. Salt-free diet for three days before observations.

Case V. Male, aged 19 years. Acute exacerbation of chronic glomerulonephritis. In 1924 he had oedema of nephritic type for six weeks. In March, 1925, following a mastoid operation, albumin, blood, and casts were found in the urine. The observations reported were made in July. Examination showed a puffy face, but no other oedema; a few fine retinal haemorrhages; apex beat in fifth space inside nipple line; blood-pressure 140/100; definite anaemia; haemoglobin 60 per cent. The urine contained 0.1 per cent. albumin, and varying numbers of red cells and casts. The blood urea was 50 mg. and the cholesterol 150 mg. per cent. After urea feeding the maximum concentration of urea was 1.8 per cent. and the maximum output 1.6 gm. per hour. The specific gravity varied from 1,001 to 1,020. There was therefore evidence of a mild grade renal insufficiency. Salt-free diet was given for a long period before the observations were made.

Case VI. Male, aged 34 years. Chronic hydraemic nephritis (nephrosis). In 1925 his legs and feet swelled and the urine was found to contain a large amount of protein. There never was great swelling and there have been no other symptoms. In 1925, at the time of the observations, the face was pale and puffy, but there was no oedema elsewhere; he took a salt-free diet for ten days before this and lost eight pounds in weight. Heart: apex beat in fifth space inside nipple line; sounds natural. Blood-pressure 120/75, and has at no time been observed above normal. Haemoglobin 92 per cent. Urine: 0.8 per cent. protein, occasional red cells, few hyaline granular and fatty casts. W. R. negative. Blood urea 30-40 mg., not increased by urea therapy. Urea concentration test, 2.5 per cent. and 2.5 gm. per hour. Blood cholesterol 400 mg. Range of specific gravity, 1,002 to 1,022.

Case VII. Male, aged 21 years. Subacute hydraemic nephritis (nephrosis). General oedema followed an attack of diarrhoea and vomiting. On admission three weeks later the oedema had diminished, but was still obvious. Retinae showed some pallor but no retinitis. Heart: apex beat in fifth space, four inches from mid-line; sounds natural. Blood-pressure 128/78. Spleen slightly enlarged. No ascites. The urine appeared clear; it contained 1 per cent. of protein and the deposit consisted of numerous hyaline casts and a few leucocytes. Blood urea 20 mg., blood cholesterol 310 mg. Haemoglobin 96 per cent. W. R. negative. Thrombosis of the femoral vein was followed by massive oedema of the leg. The acid was given ten days after this event. Four months later he was discharged with slight oedema of the ankles and 0.05 per cent. of protein in the urine. A year later his recovery was complete.

Case VIII. Male, aged 49 years. Chronic interstitial nephritis. Quite well till December, 1925, when he suddenly lost the sight of his right eye. There was a history of gout and alcoholic excess. Examination showed the apex beat to be in the fifth space, $4\frac{1}{2}$ in. from the mid-line, and to have a heaving character; the second aortic sound was accentuated. The blood-pressure was 260/140. The eyes showed severe arteriosclerotic retinitis, and the right eye acute glaucoma.

The urine contained a trace of protein and many hyaline and granular casts; a few red cells. Haemoglobin 75 per cent. W.R. negative. There had been no oedema. The blood urea, which was 165 mg. per cent. in December, had fallen to 72 mg. by the middle of January, when these tests were applied. Salt-free diet was given three days before the control period.

Case VIII a. Male, aged 50 years. Chronic interstitial nephritis. He had a haemoptysis in December, 1924. In February, 1925, vision became indistinct. On admission he was found to have severe arteriosclerotic retinitis. The apex beat was felt in the fifth space, $4\frac{1}{2}$ in. from the mid-line, in spite of considerable emphysema. Blood-pressure 205/135. Urine contained a trace of protein but no red cells or casts; the highest specific gravity observed was 1.030. Blood urea 45 mg. The urine determinations were falsified by incomplete collections, as shown by the creatinine excretion, and were rejected. The diet was not salt free.

Case IX. Female, aged 41 years. Chronic glomerulo-nephritis, azotaemic type. In 1918 she suffered from general oedema, headaches, and dyspnoea. Since then she had not been well and oedema had recurred frequently. Since 1923 there had been frequent vomiting. In March, 1925, she was thin and pale, but without oedema except for a little pitting of the shins. The apex beat was forcible, situated $3\frac{1}{2}$ in. from the mid-line in the fifth space; second aortic sound ringing. Blood-pressure 230/140. Well-marked arteriosclerotic retinitis. The urine contained 0.8 per cent. of protein, many hyaline and granular casts, and a few red cells. W.R. negative. Haemoglobin 80 per cent. Blood urea was 100 mg. before the period of observation and 75 mg. two weeks later. After urea feeding there was a maximum concentration of 1.5 per cent. and a maximum excretion of 0.6 gm. per hour. The specific gravity of the urine varied from 1.001 to 1.013. A salt-free diet was given for three days before the control period. She took the acid without difficulty, but vomited on the days following; as there had been no vomiting for three weeks before this it must be regarded as due to the acid, and probably in the light of a protective mechanism. She was still alive in September, 1926, and her condition had altered very little.

Case X. Female, aged 41 years. Chronic glomerulo-nephritis, azotaemic type. In 1915 she suffered from chronic parenchymatous nephritis, with general dropsy, which persisted for two years. She improved, and remained apparently well till January, 1925, when she had a haemorrhage into the conjunctiva; in June she had severe headaches and vomiting; in September a small cerebral haemorrhage caused diplopia, and a blood-pressure of 280/150 was discovered. In December another stroke caused a facial paralysis. In January, when the observations on acid excretion were made, she was very pale, with a muddy complexion; squint and paresis of the right side of the face were persisting. The apex beat was forcible, but not heaving, and was situated in the fifth space, four inches from the mid-line. There was a harsh systolic murmur at the apex and the aortic second sound was ringing. Blood-pressure 188/110. There were no retinal changes except pallor and slight thickening of the vessels. No oedema. Haemoglobin 38 per cent. W.R. negative. The urine contained 0.1 per cent. of protein, a few red cells and renal epithelial cells, and numerous granular casts. The blood urea was 156 mg. just before the acid was given, and 150 mg. just after. A salt-free diet was given for five days before the control period. She vomited on the last day of the acid period and on the subsequent day she was rather ill. She went home somewhat improved, but was readmitted in March in a moribund condition, and died with a blood urea of 570 mg.

At the autopsy the heart was found to weigh $13\frac{1}{2}$ oz. The left ventricle was considerably hypertrophied. The kidneys were small, pale, and granular; right $2\frac{1}{2}$ oz., left $3\frac{1}{2}$ oz. The cortex was about half its normal thickness; it showed yellow dots and streaks, and appeared greatly disorganized. Sections showed a late stage of glomerulo-nephritis. In parts the interstitial tissues were

infiltrated by masses of small round cells and with fibrous tissue. In these areas many of the glomeruli had disappeared, and of the remainder many had undergone hyaline degeneration. Others showed shrinking of the tufts with increase of their nuclei and adhesions to the capsule. The tubules in these areas were widely separated, but in other parts there were many dilated tubules lined by flattened cells. Many of them contained desquamated cells. The arteries and arterioles were greatly thickened.

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HEREDITY IN SIMPLE GOITRE¹

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Introduction.

THE importance of heredity in the aetiology of simple goitre² has been recognized for a considerable time, but the precise estimation of the significance of inherited predisposition in this complaint is by no means easy. Many observers have noted that in areas in which goitre is endemic, some families appear to suffer more than others, but where the incidence of goitre is high, the probability is great that multiple cases will appear in families as a result of exposure to the same environment, and not necessarily in consequence of participation in a common inheritance. This disease therefore presents a fascinating problem in the relative importance of heredity and environment.

The object of this paper is to report the histories of six families, containing among them twenty-six cases of simple goitre, and five families containing twelve patients in whom simple goitre is associated with congenital deaf-mutism, and to discuss the possible significance of the hereditary factor. The history of one family is included in the text; those of the other ten will be found in the appendices.

1. *The Middleton Cheney Family (Fig. 1).*

First generation. This family springs from Middleton Cheney, near Banbury, a village in south Northamptonshire.

I 1, Fanny B., was born there about 100 years ago. She was reported by her grandchildren to have had a considerable enlargement of her neck, probably for the greater part of her life. She died at an advanced age, some 30 years ago. Her husband was said to have been normal.

Second generation. I 1 had six children, of whom Fanny B., II 2, had a goitre and transmitted the disease to some of her children and grandchildren. She was born in 1854 at Middleton Cheney and spent the rest of her life in the neighbourhood. She died in 1923. She had a greatly swollen neck for as long as her children could remember. According to her daughter 'it hung down, more like a breast'. A photograph, in spite of a high collar and the photographer's retouching, showed a considerable enlargement of the thyroid, involving both the isthmus and the lateral lobes. Her husband (photograph seen) appeared normal. There was little information available about the other members of the second generation, but none were known to have suffered from goitre.

¹ Received October 27, 1926.

² 'Simple goitre includes those thyroid enlargements designated as epidemic, endemic, sporadic, and physiologic' (Marine) and is used in that sense in this paper.

[Q. J. M., April, 1927.]

Third generation. II 2 had ten children, all born in south Northamptonshire, four of whom had goitre, while a fifth was thought to have been affected. Martha S., III 2, the oldest affected member of the third generation, was born at Catesby, Northamptonshire, in 1872, and subsequently lived in Lincolnshire and at Leamington and Warwick. She then lived at Leamington. Her thyroid was visibly slightly enlarged and irregular, with slight prominences in the lower part of the right and the upper part of the left lobes. She did not know at what age the enlargement developed. She showed no signs of hyperthyroidism.

Michael R., III 3, is especially interesting, owing to the rarity of the appearance of hereditary goitre in the male sex. He was born at Catesby, Northamptonshire, in 1875, but had come to London as a young man and had since lived at Plaistow. His neck had been swollen as long as he could remember. There was a diffuse enlargement of the thyroid in which could be seen and felt five localized masses. He showed no signs of hyperthyroidism.

Annie S., III 6, was born in 1883 at Fawsley, Northamptonshire, where she lived till 1901, when she moved to London, moving again three or four years later to Birmingham, where she had lived ever since. She first noted an enlargement of the neck when she was about 20 years of age. She had a large central adenomatous cyst, the circumference of her neck at the largest part being 15½ inches. She showed no signs of hyperthyroidism.

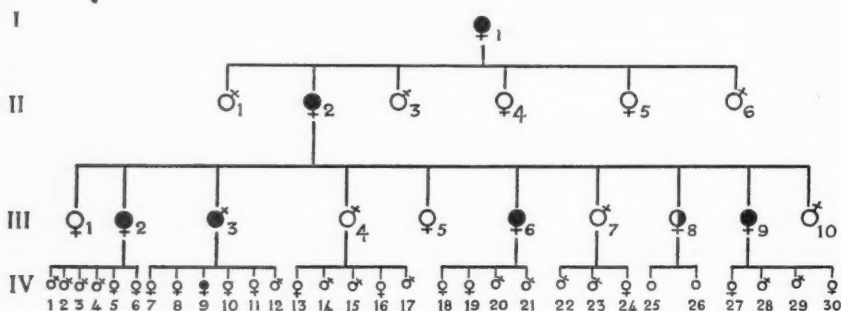


FIG. 1.

Ruth Y., III 9, was born in 1886 at Eydon, Northamptonshire, where she lived till 1915. She had since lived at Wilford, Notts. (1915-20), Nottingham (1920-25), and Grimsby, where she then resided. I have been unable to examine this patient, but she wrote that her neck was swollen, the circumference being 15 inches. She did not remember when the swelling first appeared. She did not suffer from prominence of the eyes, palpitations, or nervousness.

Of the other members of this generation, Fanny R., III 1, died at the age of 40 and was said to have been normal. Frederick R., III 4, and Martin R., III 7, wrote that they had no swelling of the neck; and the addresses of Ellen S., III 5, Rhoda R., III 8, and Frank R., III 10 were not known to their relations. Michael R., III 3, stated that he had heard that Rhoda R., III 8, had a goitre, but nothing was known about the other two.

Fourth generation. I have examined eleven members of the fourth generation and seen photographs of four others; concerning fourteen I have received reports from their parents; nothing was known about the remaining one. Six were under the age of 10 years. Only one member of the fourth generation was known to have enlargement of the thyroid.

Rhoda R., IV 9, was the third child of Michael R., III 3, an affected member of the family. Her mother had no enlargement of the thyroid. She was born

at Plaistow in 1908 and had lived there all her life. Her neck was first noticed to be swollen when she was 17 years of age. She had a slight visible enlargement of the thyroid, without signs of hyperthyroidism.

A survey of the incidence of goitre among school children in Northamptonshire was made in 1924 (13), but unfortunately the village from which this family springs was not included, as it had been inspected a short time previously. In the whole county 2,025 children aged 12 years were examined. It was found that in the urban districts 1.5 per cent. of the boys and 7.6 per cent. of the girls were affected, while in the rural districts the proportion affected was 4.2 per cent. of the boys and 10.2 per cent. of the girls. Clearly Northamptonshire must be regarded as a county in which goitre is to some extent endemic.

Evidence for the Existence of Hereditary Predisposition in Goitre.

In the six families in the first series in this paper, there were found twenty-six cases of simple goitre, there being in one instance seven cases in one family, distributed over four generations. All six families spring from rural districts in England in which goitre is to some extent endemic, namely, two from south Northamptonshire and one each from Durham, Norfolk, Suffolk, and Bedfordshire. It is necessary, therefore, first to consider whether the familial incidence may not be explained as due simply to exposure to a common environment which contains the external factor or factors responsible for inducing goitre. Several considerations render this view untenable:

(1) Certain families inhabiting areas in which goitre is endemic exhibit a much higher incidence of the complaint than the average obtaining in the neighbourhood.

(2) Members of such families may develop goitre, although they themselves have been born and brought up in areas in which goitre is not endemic.

(3) Hereditary goitre is known to occur sporadically in areas free from endemic goitre.

(1) The table below shows the proportion of persons affected in the families in the first series, i. e. those exhibiting simple goitre only, including only those in which the number of siblings was ascertained.

Sex.	Total Siblings.	Number affected.	Percentage.
Male	20	2	10.0
Female	30	14	46.6
Unknown	13	2 (both females)	—
Total—both sexes	63	18	28.5

Owing to the small numbers, little stress is laid on these figures, but it appears that nearly 50 per cent. of the female members of these six families were affected, an incidence higher, as far as can be ascertained, than that reported in females at any age in any area in England, and probably very much higher than the average for the areas concerned, which are not among those in which goitre is most rife.

Milligan (7) has reported twenty-six cases of goitre occurring in four generations of the family of a goitrous woman resident at Glossop, Derbyshire. In this family there were twenty-five females and fourteen males. All the female members and one male were affected.

(2) Four affected persons in this series, members of families which had shown a high incidence of goitre while living in areas in which it is endemic, developed goitre although they had been born and brought up in London, where goitre is not endemic. It is, however, of interest that in one of these cases the enlargement of the thyroid was first noticed shortly after the patient's return from a visit of three months' duration to the family home in Suffolk.

(3) Siemens (9) and Bluhm (1) have both described families living in areas in which goitre is not endemic and yet manifesting goitre in many generations. In Siemens's family there were nine cases in six successive generations, while Bluhm reports no less than fifteen cases in four generations of the same family.

Sheasby (8) has reported the familial occurrence of goitre at Cardiff. Cardiff is an area in which goitre is rare, for of 12,013 school children examined in 1920, only 67, or 0.55 per cent., had enlarged thyroids. Inquiry as to the family history was made in the case of 23 of the affected children. Of these, 17 possessed among them 28 relatives similarly affected.

The above facts indicate that, in the cases quoted, environment cannot alone account for the development of goitre, and suggest that some internal factor, which may be called predisposition, must play a part, the inheritance of such a predisposition accounting for the high familial incidence of the complaint. It is well known, however, that maternal goitre is frequently the cause of goitre in the new-born child. It is necessary to consider whether the assumption of inherited predisposition is really required, or whether the transmission of goitre from one generation to another may not be due simply to the influence of maternal goitre during antenatal life. There is evidence that maternal goitre may be responsible for activating the inherited predisposition in the child, and this will be considered later. Such antenatal influence is not, however, sufficient to account for the transmission of the complaint. It might be difficult to establish this if hereditary goitre were transmitted only by the female sex. Transmission through the father, though apparently less frequent, certainly occurs. It was noted once in the present series, and twice in Bluhm's family; while Sheasby (8) has reported one instance, and Stacey (11) three. In the family reported by Milligan (7) the complaint was transmitted through the father in five instances. The occurrence of paternal transmission is sufficient to establish that the predisposition must form a part of the germinal material. This is supported in an interesting manner by the observations made by Siemens (9) on goitre in twins, in the course of his researches on the diagnosis of uniovular and binovular twins by dermatological and other methods. Of forty-one pairs of uniovular twins examined, forty resembled each other in respect of the presence or absence of goitre, and in its appearance and size when present, as it was in sixteen pairs. In only one pair was any difference noted between the twins, one twin having

an easily palpable thyroid, and the other a slight parenchymatous goitre. Of twenty-nine binovular twins examined as controls, only thirteen pairs showed a resemblance in respect of the condition of the thyroid, in sixteen there was a difference. Similar results were obtained by Weitz (14) in a series of forty pairs of uniovular twins. These facts demonstrate the importance in the aetiology of goitre of the hereditary factor as distinct as from both antenatal and postnatal environment, since the twins of the two groups differed only in respect of their germinal material. This is the same for each of a pair of uniovular twins, but different when twins are binovular.

The Relationship of Predisposition and Environment.

The fact that all six families in the first series spring from districts in which goitre is to some extent endemic indicates that environment also is of aetiological importance. This aspect must now be considered. The view of the aetiology of simple goitre now most generally held is that it is due to lack of iodine. This view has been established largely through the researches of Marine and his collaborators. A most important confirmation of it has recently been provided by Hereus, Benson, and Carter (4), who have made a survey of the iodine content of the soil and water throughout New Zealand and have been able to correlate this with the incidence of goitre in school children and army recruits. These authors found that the incidence of goitre in a district was in inverse relationship to the iodine content of the soil, except that in some areas where the incidence of goitre was low, in spite of a low iodine content in the soil, this was accounted for by an exceptionally high iodine content in the water.

The aetiological importance of infection stressed by McCarrison would appear to be capable of reconciliation with the theory that the disease is due to lack of iodine, if it be supposed that infective organisms may interfere with the absorption of iodine, either by fixing it, or by rendering the mucous membrane of the intestine incapable of dealing with it. Can the established facts concerning the existence of an inherited predisposition be brought into relation with the hypothesis of the aetiological importance of lack of iodine? Siemens (9) draws a distinction between the hereditary factor in 'sporadic' goitre, i.e. goitre occurring in families not resident in goitre areas, and in endemic goitre. The former he calls 'idiotypical', the latter 'idio-dispositional'. This distinction would seem to be unnecessary, or to be at least relative and not absolute. For the two classes may be regarded as suffering from different degrees of disturbance of iodine utilization. In hereditary 'sporadic' goitre it is suggested that iodine utilization is so defective that the amount derived from a normal environment is inadequate to prevent goitre. Families exhibiting an abnormally high incidence of the disease in goitre areas only may be regarded as suffering from an inherited defect of iodine utilization which is less pronounced than in the former class and only manifests itself in an environment in which the available supplies of iodine are less than normal, though the shortage is insufficient to cause

goitre in persons not predisposed. Between these two groups there is on this hypothesis merely a difference of degree in respect of their capacity for iodine utilization.

Sex Differences in Incidence and Transmission.

It will be noted that hereditary goitre affects women much more frequently than men. In the families reported by Siemens and Bluhm, twenty-four women were affected and there was only one doubtful case in a man. This led Siemens in his first communication (9) to conclude that there was manifest a 'dominant sex-limited mode of inheritance with absolute (or practically absolute) limitation to the female sex'. Subsequently, however, he modified his conclusion by stating that this sex-limitation held good only for some forms of sporadic goitre (10). The first series of twenty-six cases reported in this paper includes two affected males; three have been reported by Stacey (11), and one each by Sheasby (8), Bluhm (1), and Milligan (7). There does not seem any justification for Siemens's assumption that there are different forms of sporadic goitre, some only of which are sex-limited. We must rather conclude that the appearance of sex-limitation was due to the smallness of the numbers considered, and that if a sufficient number be taken, affected males are found to be included. Goitre is therefore not a sex-linked character, and we must attribute the preponderance of females over males among those affected not to the character of the germinal inheritance, but to some other factor. It has been noted that in endemic goitre the sex incidence varies according to the severity of the endemic. 'Where the endemicity is slight, cases may be met with only among women; but in regions of high endemicity the proportion of men to women affected may approximate as closely as one to one' (McCarrison (6)). The same author states that 'female animals have more thyroid tissue and more iodine therein per unit of body-weight than males'. It is not surprising therefore that females should be more susceptible than males to iodine shortage, whether that be due to an absolute shortage of iodine in the environment, or an inherited defect of the utilization capacity of the individual. It is interesting that the sex ratio in inherited goitre should be that characteristic of areas of slight endemicity, i. e. where the iodine shortage in the environment is insufficient to affect males. It may be assumed therefore that the handicap in respect of iodine utilization present in patients with hereditary goitre is about the same as the normal handicap of women compared with men, which is demonstrated in areas of slight endemicity. If it were more severe than this, it would seem likely that men would be more frequently affected. Not only does hereditary goitre affect women to a much greater extent than men, but it is also transmitted by women apparently much more frequently than by men. If this conclusion were based on statistics such as those collected in the course of school inspections, it might be fallacious. For if the predisposition becomes manifest in women much more frequently than in men, even though it were transmitted equally by both sexes, the father would often be unaffected. Maternal trans-

mission therefore would predominate in the statistics. This objection does not apply to figures based on complete family genealogies where it is possible to trace the offspring of the male members of the family for several generations. If the families reported by Siemens and Bluhm be grouped together with those in the first series, it is possible to form some idea of the relative frequency of transmission of the complaint by affected and unaffected persons of the two sexes. In the eight families fifty persons had children. The numbers in the different categories transmitting the complaint are as follows :

Group.	Affected Males.	Normal Males.	Affected Females.	Normal Females.
Number in Group	1	18	20	11
Number transmitting complaint	1	3	16	4

These numbers are small, but it is evident that, taking affected persons and normals together, females transmit the complaint more often than males. The number of affected males is too small for comparison with the normals, but it appears that affected females transmit the complaint more often than those apparently healthy. Any explanation of this must necessarily be speculative, but it is suggested that the difference between the two sexes in respect of transmission may be apparent only, the predisposition being transmitted equally by either sex, and becoming manifest more frequently in the children of affected females owing to the influence on the foetus of the established disturbance of thyroid function in the mother.

The Association of Simple Goitre and Congenital Deaf-mutism.

Through the kindness of Mr. A. J. Walton I am able to include in this paper an extremely interesting series of twelve of his patients, belonging to five families, who exhibit the familial occurrence of simple goitre associated in every case with deaf-mutism. Apart from the association with deaf-mutism, there are certain striking differences in the mode of manifestation of the goitre between the families of this second series and those of the first. Four of the families of the second series are resident in the East End of London, where goitre is not endemic; the fifth resides at Sheerness. Environment therefore would not seem to play an important part in the development of the disease. Males are affected almost as frequently as females. Of the twelve affected persons, four are males, six females, and two of unknown sex. Finally, the complaint is in every family confined to one generation; the parents being normal and there being no record of any previous case of goitre or deaf-mutism in the family histories. It is apparent that though in these cases the familial incidence of goitre must be attributed to the presence of an inherited predisposition, this predisposition behaves quite differently in transmission from the hereditary factor which is assumed to be present in the patients of the first series. This difference will be discussed in the next section.

McCarrison (6) has noted a relationship between deaf-mutism and cretinism. 'Eighty-seven per cent. of all cretins', he says, 'are deaf-mutes in greater or lesser degree. In the majority the deaf-mutism is complete; in the minority it is partial. In the nervous type it is almost always complete, less frequently so in the myxoedematous. The defect may be caused in part by the infiltrated condition of the tongue, aural mucosa, Eustachian tubes, and naso-pharynx, but it is mainly dependent on imperfect development as well as on infiltration of the higher brain centres and on the lack of receptivity of the nerves.' It is clear that in cretins deaf-mutism is secondary to the disturbance of thyroid function. The patients in the present series, however, were not cretins. They showed neither defect of intelligence nor infantilism, and the deaf-mutism was congenital, while the goitres did not develop until the second, or late in the first decade of life. The association of deaf-mutism and goitre in these patients is probably due to an association in the germinal material of the hereditary factors responsible for them.

Simple Goitre and the Mendelian Laws of Inheritance.

Mendelian laws are concerned with the numerical proportions in which transmitted characters are manifested in the offspring. At least three requirements must be satisfied before conclusions regarding such laws can be drawn from clinical material. The presence or absence of the inherited character must be capable of ready determination. The number of cases must be large enough to exclude statistical errors; and the manifestation of the character must not depend on variable environmental factors. Unless the third condition is fulfilled, no uniformity is to be expected in the manifestation of the character in question and no valid conclusion can be drawn as to its mode of transmission. If the view put forward above as to the role of the environment in the aetiology of inherited goitre be correct, variations in the environment might determine whether the inherited predisposition should be manifest or latent; hence it would be impossible to be sure that the affected members of a family included all who had inherited the predisposition. The families reported by Siemens and Bluhm inhabited areas in which goitre is not endemic. If we may assume that in these cases the environment played no part in the aetiology of the goitre, this material would be suitable for consideration by Mendelian methods. In these families the evidence on the whole supports Siemens's contention that the predisposition to sporadic goitre is inherited as a Mendelian dominant. There appear to be no grounds for his suggestion that the predisposition to endemic goitre is inherited as a Mendelian recessive, and if the contention put forward above, that there is no difference in kind between hereditary sporadic and hereditary endemic goitre, is valid, it is probable that hereditary endemic goitre will also be inherited as a Mendelian dominant. If we allow for the variable environmental factor, the incidence of the complaint in the first series of families reported in this paper supports this view.

In the families of the second series strong evidence that heredity is of aetiological importance is afforded by the association in every case of goitre with deaf-mutism, which is well known to be hereditary. But the occurrence of the complaint in the offspring of normal parents suggests the presence of a recessive factor in both parents, who transmit the complaint without themselves manifesting it. This view is supported by the fact that congenital deaf-mutism appears also, from a consideration of reported family histories (12), to be inherited as a Mendelian recessive. We are faced therefore with the conclusion that the same clinical condition, simple goitre, may be inherited in some families as a Mendelian dominant and in others as a Mendelian recessive. This is not necessarily inconsistent with Mendelian principles, but illustrates the complexity of the conditions determining the inheritance of pathological characters. It has been pointed out earlier in this paper that the available evidence strongly suggests that simple goitre is due to lack of iodine. It is probable that this lack may arise in different ways. It may be due to an actual shortage of iodine in the environment, or it may depend on a relative inability on the part of the individual to absorb or utilize iodine: or both factors may be present. This hypothesis suggests a possible explanation of the occurrence of two different modes of inheritance of simple goitre. We may suppose that more than one form of inherited defect of iodine utilization can occur. Clinically we cannot at present distinguish one form of defect from another, though an increase in our knowledge of iodine metabolism may enable us to do so. We find, however, that the disturbance of function which leads to simple goitre may be inherited as either of two unit characters which behave quite differently in transmission. One, probably a Mendelian dominant, affects successive generations, is manifested by females much more often than by males, and may be latent in the absence of a shortage of iodine in the environment. Another, probably a Mendelian recessive, appears in several children of normal parents and in the absence of a family history of the complaint. It is manifested by males and females equally, and in the presence of a normal supply of iodine, and in the cases reported is associated with the hereditary factor for congenital deaf-mutism. These differences may perhaps be explained if we suppose that what is inherited is not, strictly speaking, goitre, but two different forms of defect in the processes of iodine utilization. In other words, there are probably many hereditary factors, or genes, which influence iodine utilization, and as many possible hereditary disturbances of it. More than one such disturbance may be manifested clinically as goitre. The idea that one manifest character may be influenced by many genes receives support from experimental genetics.

The association of congenital deaf-mutism with goitre may probably be regarded as an example of linkage in human inheritance. Another instance of an hereditary character linked with goitre has been described by Fürst (3). In investigating the inheritance of goitre by the children of parents, one of whom was affected, he found that the goitre appeared only in those children who inherited the blood group of the affected parent.

The Importance of Heredity in the Aetiology of Goitre.

It is natural to inquire, in conclusion, whether hereditary predisposition is a common, or merely an exceptional factor in the aetiology of simple goitre. The present investigation does not provide an answer to this question. But it is suggestive that six affected families should have been met with in a short time in the course of the routine examination of medical patients at a London hospital. No investigation appears to have been made in this country into the incidence of goitre in the families of affected persons, except that Sheasby (8) noted at Cardiff that in twenty-three cases in which inquiry was made, a family history of the complaint was obtained in seventeen. Lloyd (5) in the United States has collected information from larger numbers. At St. Louis 100 unselected patients with goitre yielded data concerning 2,781 relatives of whom 248, or 8.9 per cent., suffered from goitre, compared with 3 per cent. affected in the general population. At Chicago 100 cases giving a family history of the complaint were chosen. From these information was obtained concerning 640 relatives of whom 38 per cent. were goitrous. In the St. Louis series females outnumbered males in the proportion of 8 to 1. In neither series is the percentage of goitre patients with affected relatives given, but it is a striking fact that an unselected series of 100 patients should possess almost 250 affected relatives and that the incidence of goitre among their relatives should be practically three times that in the general population. It is to be hoped that similar investigations will be conducted in this country, and, particularly, that the percentage of patients with goitre having affected relatives will be noted. Until this is done, the importance of hereditary predisposition in the aetiology of the complaint cannot be estimated.

Summary.

1. A series of six families is reported, including among them twenty-six cases of simple goitre. In two of these families cases occurred in four successive generations.
2. A second series of five families is reported, containing twelve cases of simple goitre associated with congenital deaf-mutism.
3. Evidence is brought forward in support of the view that hereditary predisposition is a factor in the aetiology of simple goitre in some cases.
4. The relation of predisposition and environment in such cases is discussed.
5. An explanation of the differences between the sexes in respect of the incidence and transmission of goitre is suggested.
6. The inheritance of goitre is considered in relation to Mendelian laws.
7. It is concluded that simple goitre may be the manifestation of more than one abnormal hereditary factor, two of which can be distinguished by their behaviour in transmission.

It is a pleasure to acknowledge the help which I have received from many sources in collecting the material of this paper. I am indebted to Mr. A. J. Walton for his generosity in allowing me to publish the histories of the families in which deaf-mutism is associated with goitre, and also the history of Family 2; to Professor Arthur Ellis for the stimulus of discussion and criticism, and for his permission to publish the history of Family 3; to Drs. L. Meredith Davies, T. Eustace Hill, J. T. C. Nash, and A. Hamilton Wood, Medical Officers of Health for the counties of Northamptonshire, Durham, Norfolk, and Warwickshire respectively, and to Drs. Ronald T. Herdman and B. Wood-White, School Medical Officers for Bedfordshire and East Suffolk, for information, in some cases specially obtained, concerning the incidence of goitre in districts under their charge; to Dr. Ernest Milligan, Medical Officer of Health for Glossop, for additional information concerning the family reported by him; and, finally, to my patients and their relatives, without whose ready co-operation and genealogical researches the investigation could not have been carried out.

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APPENDIX I.

*Families 2 to 6, containing Cases of Simple Goitre.*2. *The Houghton Regis Family (Fig. 2).*

First generation. This family springs from Houghton Regis, near Dunstable, Bedfordshire.

Hannah B., I 1, was born in this village in 1806 and died there in 1876. Her neck, according to her grand-daughter, III 6, was much enlarged.

Second generation. I 1 had seven children, of whom the youngest, Elizabeth B., II 7, a single woman, died at Rickmansworth in 1923, aged 62. According to her niece, III 6, this woman had a swelling of the neck, most noticeable on the right side. None of the other members of this generation were known to have suffered from goitre.

Third generation. The only affected member in this generation was Emily E., III 5, who was an in-patient at the London Hospital under the care of Mr. A. J. Walton, to whom I am indebted for kindly allowing me to include her and her family in this series. III 5 was the fifth of thirteen children and was born at Dunstable in 1876. She lived at Dunstable until fifteen years ago, when she moved to Luton. She first noticed an enlargement of the neck at the age of 16. The thyroid, on examination, was found to be greatly enlarged and to contain many adenomata. There was no sign of hyperthyroidism.

Fourth generation. Only one member of the family in this generation was known to be affected. IV 1, female, born at Houghton Regis in 1886, developed a swelling of the neck at puberty. A few years ago she went to live in Canada, and it was reported that the swelling had now disappeared.

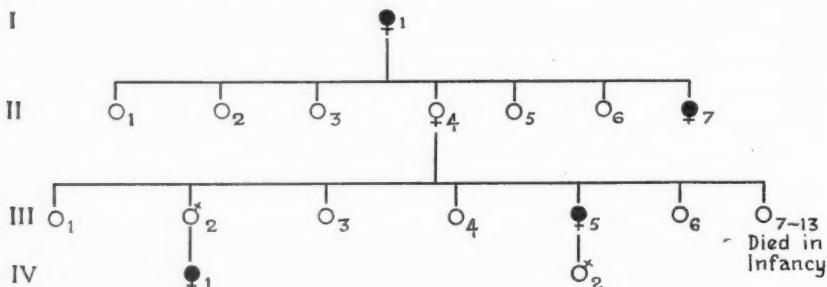


FIG. 2.

The following information as to the incidence of goitre in the Dunstable and Houghton Regis neighbourhood has kindly been furnished by the School Medical Officer to the Bedfordshire County Council Education Committee, Dr. Ronald T. Herdman:

'There is a certain amount of goitre to be found all through Bedfordshire. During the years 1924 and 1925 I found the following numbers of girls over 12 years of age at Dunstable and Houghton Regis who had enlargement of the thyroid:

1924	2 out of 12 examined at Dunstable
2	" " 12 " " Houghton Regis
1925	5 " " 40 " " Dunstable
1	" " 20 " " Houghton Regis.

'There are certainly some parts of Bedfordshire that are worse than Houghton Regis and Dunstable in this respect.'

3. The Houghton-le-Spring Family (Fig. 3).

First generation. This family had resided at Houghton-le-Spring, County Durham, for several generations.

Margaret R., I 1, developed a swelling of the neck comparatively late in life. Her husband was normal.

Second generation. I 1 had seven children, none of whom were known to have suffered from goitre.

Third generation. In this generation adenoma of the thyroid occurred in two out of the five children of II 7, who was herself reported to be normal.

Ethel R., III 2, was born at Houghton-le-Spring in 1897. She first noticed a swelling of the neck at the age of 14. She gradually developed a swelling the size of an orange in the middle line, and a smaller one on each side. A photo-

graph taken at the age of 17 showed a marked irregular enlargement of the thyroid. She was operated upon at the age of 23 and stated that 'five swellings were taken away from her neck'. Later she went into the London Hospital under the care of Professor Ellis, to whom I am indebted for permission to include her in this series.

Edward R., III 3, born at Houghton-le-Spring in 1902, began at the age of 12 to develop a swelling of the neck, which grew almost to the size of a golf ball and was situated on the left side. He was operated upon in the Royal Infirmary, Sunderland, at the age of 14, the condition found being 'an adenomatous goitre'.

Annie G., III 1, born in 1896, was said to be normal and, in a photograph, the neck did not appear to be enlarged.

Henry R., III 5, born in 1908, was also said to be normal.

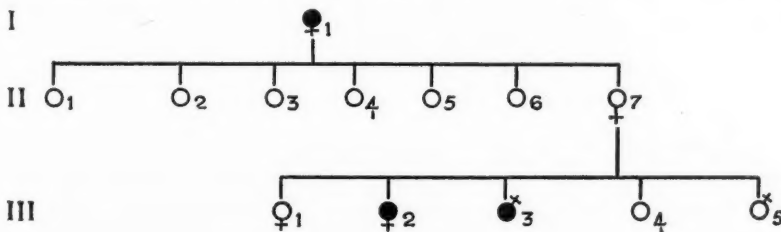


FIG. 3.

The Medical Officer of Health for the County of Durham, Dr. T. Eustace Hill, has kindly furnished the following information as to the incidence of goitre in the neighbourhood of Houghton-le-Spring:

'From the figures from recent medical inspections by one of my assistants, I am able to give you the following information regarding the incidence of adenoma of the thyroid and other forms of goitre in Houghton-le-Spring district. The figures relate to children of 12 and 13 years of age, and show a very low incidence of goitre amongst the boys in the schools around Houghton and a somewhat higher incidence amongst the girls, the latter being no doubt attributable to the physiological enlargement which often occurs at about this age.

'My Assistant Medical Officer tells me that she has never found goitre to be prevalent in the Houghton district during all the years she has worked in it. There are, of course, some parts of the county, as for instance certain parts of the Wear Valley, which are definitely goitrous areas, but Houghton-le-Spring district has never been regarded as one of these.'

Dr. Eustace Hill has been kind enough also to send me information supplied by Dr. Margaret A. Reid, Welfare Medical Officer in charge of the Maternity and Child Welfare Centre in the Houghton-le-Spring area. Dr. Reid states that there is not a great prevalence of adenoma of the thyroid in that neighbourhood, but reports one family in which a mother and three daughters are affected.

4. The Stowmarket Family (Fig. 4).

First generation. This family comes from Stowmarket, Suffolk. I 1 and I 2 were said to be normal.

Second generation. Elizabeth B., II 1, was born and lived at Stowmarket, where she died at the age of 68 of diabetes. She was said by her daughters to have had 'a very large neck' and to have had special collars made to cover it.

Esther H., II 2, a younger sister of II 1, also had a large neck, which was first noticed when she was a child. She was born at Stowmarket in 1859 and

later moved to Eltham, where she then lived. "She wrote that the circumference of her neck was 16 inches and that she did not suffer from prominent eyes, palpitations, or nervousness. II 3, II 4, and II 5, a sister and two brothers of these patients, were normal.

Third generation. II 1 had eleven children, all born at Stowmarket, Suffolk. Two of these had goitre.

Caroline P., III 1, born in 1879, first noticed a swelling of the neck at the age of 23. The circumference of her neck was $14\frac{1}{2}$ inches.

Eleanor D., III 7, born in 1887, had noticed the enlargement for only three years. She had a localized enlargement of the left lobe of the thyroid, the size of a walnut, and was without symptoms of hyperthyroidism. Both these patients moved from Suffolk at the time of their marriages to London, where they resided. All the other members of this generation are normal.

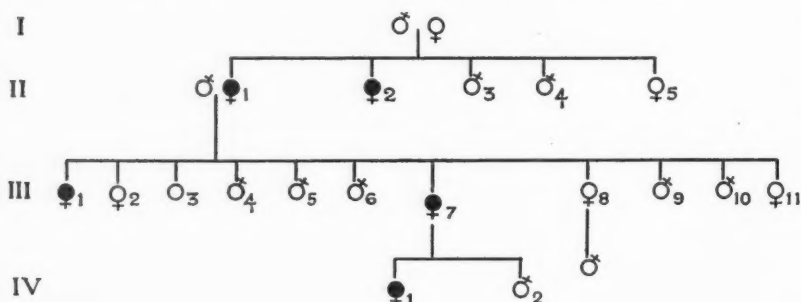


FIG. 4.

Fourth generation. One member of this generation was known to be affected. IV 1, female, born in London in 1909, had a visible slight enlargement of the thyroid, which was first noticed when she was medically examined for a Civil Service appointment at the age of 16. It is interesting that she had just returned from a stay of three months' duration at the family home at Stowmarket. She showed no signs of hyperthyroidism. Her brother, IV 2, was normal.

The School Medical Officer for East Suffolk, Dr. B. Wood-White, has kindly furnished the following information concerning the incidence of goitre in Stowmarket:

'I find from my records that cases of goitre are no more common in Stowmarket than in East Suffolk generally, but that the complaint is largely spread throughout the county.'

Dr. Boul (2), Assistant School Medical Officer, investigated the incidence of goitre in East Suffolk in 1923, and found that enlargement of the thyroid was present in 5.8 per cent. of 3,764 girls of school age, and in 1.33 per cent. of 2,133 boys of school age. It should be added that he considers that in 3.5 per cent. of the girls and 0.6 per cent. of the boys, the enlargement of the thyroid is associated with symptoms of hyperthyroidism.

5. The Greatworth Family (Fig. 5).

First generation. This family springs from Greatworth, Northants, a village only a few miles from Middleton Cheney, the home of Family 1. It has not, however, been possible to trace any relationship between them. I 1 and I 2 were both normal, I 2 being then still alive and 93 years of age.

Second generation. Mrs. B., II 9, was the only member of this generation affected. She was born at Greatworth in 1873 and had moved to London at the age of 20. She noticed that she had a swelling of the neck only a year or two ago. She exhibited a moderate general enlargement of the thyroid, the lower part of the left lobe being especially prominent. She showed no signs of hyperthyroidism.

Of the remaining ten children of I 1 and I 2, II 2, II 7, and II 10 died of 'consumption'. The others, all females, were well, and did not suffer from enlargement of the thyroid.

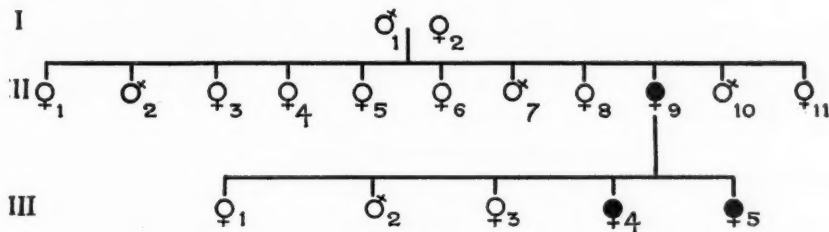


FIG. 5.

Third generation. II 9, the only affected member of the second generation, had five children, two of whom had goitre.

Doris B., III 4, aged 20, according to her mother had a large throat for years. She refused to come to hospital for examination.

Phyllis B., III 5, was referred to hospital by the school medical officer on account of goitre. She showed a moderate general enlargement of the thyroid, the right lobe being especially prominent. She showed no signs of hyperthyroidism.

III 1, III 2, and III 3 were reported to be normal. All the five children of II 9 were born and had spent their lives in London.

A report on the incidence of goitre in Northamptonshire will be found at the end of the history of Family 1.

6. The Hindolveston Family (Fig. 6).

First generation. In this family the complaint was confined to one generation in which four out of seven siblings were affected. The four oldest were born at Hindolveston, Norfolk, and the three youngest at the neighbouring village of Foxley. All the affected members were females. I 1 and I 2, the parents, were alive and well, aged 53 and 55 respectively; neither suffered from goitre.

Second generation. Ellen E., II 2, was 32 years of age. She was born at Hindolveston and then resided at Francham, near Dereham. Her neck had been swollen since the age of 14.

Emma B., II 3, aged 28, was born at Hindolveston and had moved to Leyton on her marriage. She had had a moderate enlargement of the thyroid as long as she could remember. She showed no signs of hyperthyroidism.

Emily G., II 4, aged 26, was also born at Hindolveston and lived at East Dereham. She also was reported to have a swelling of the throat.

Lilian H., II 6, aged 24, was born at Foxley, near Dereham, and had moved on her marriage to Leytonstone. She had a localized swelling of the thyroid, the

size of a walnut, in the middle line. This she had had as long as she could remember. She showed no signs of hyperthyroidism.

II 1, II 5, and II 7 were reported to be normal.

Third generation. No member of this generation was more than 8 years of age and all were normal.

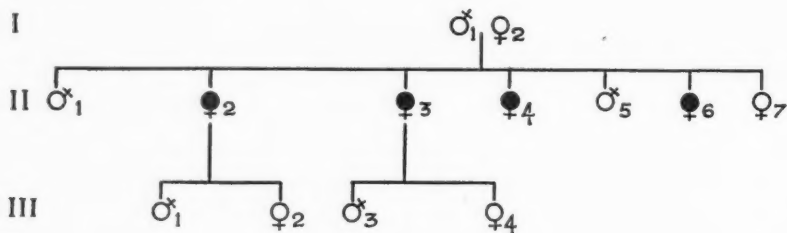


FIG. 6.

Dr. J. T. C. Nash, County Medical Officer of Health for Norfolk, has kindly furnished information as to the incidence of goitre in the neighbourhood of Dereham. At Foxley no cases were noted among the village residents. At Hindolveston, out of 74 children examined, 8 or 10.9 per cent. were goitrous. Dr. Nash states that 'the information at my disposal through school medical inspection certainly seems to indicate that some villages in Norfolk are goitrous, apart from physiological enlargement of the thyroid associated with puberty'.

APPENDIX II.

Families 7 to 11, containing Cases of Simple Goitre associated with Congenital Deaf-mutism.

(Mr. A. J. Walton's Cases.)

7. The Poplar Family.

In this family, resident in the East India Dock Road, the parents were normal and there was no history of goitre or deaf-mutism in the family. There were three children, all congenital deaf-mutes and all goitrous. One, a girl, died following an operation for goitre. A brother had also been operated upon for goitre. The patient, Joseph M., aged 26, suffered from a large adenomatous cystic goitre. Mr. Walton at operation removed a large wedge of adenocystic tissue from both lobes of the thyroid.

8. The Plaistow Family.

This family lived in Plaistow. Both parents were normal and there was no family history of deaf-mutism or goitre. There were six children. The two oldest, both male, were normal.

Alfred E., the third, was a deaf-mute. He showed an enlargement of the right lobe of the thyroid, and Mr. Walton performed a wedge-resection.

The fourth child, female, was also a deaf-mute. She developed a swelling of the neck at the age of 14, and when seen two years later showed a nodular enlargement of the thyroid.

The fifth and sixth children were twins, both female. One was normal; the other, Emily E., was a deaf-mute who began to suffer from swelling of the neck at the age of 11. When seen eight months later she showed a diffuse enlargement of the thyroid.

9. *The Sheerness Family.*

In this family, resident at Sheerness, there was no history of goitre or of deaf-mutism, and the parents were normal. There were three children, all deaf-mutes and all goitrous. The goitres were said to have developed at about the age of 6 in each case. The only child examined was Florence B., who at the age of 12 was found to have two adenomata of the thyroid, one in the isthmus and one in the left lobe. These were excised by Mr. Walton.

10. *The First Bethnal Green Family.*

There was no family history of goitre or deaf-mutism. Both parents were normal.

There were six children, two of whom were both deaf-mutes and goitrous. The three oldest, all males, were well.

The fourth, Rose S., aged 15, a deaf-mute, developed a swelling of the neck at the age of 14 and was found to have a small simple goitre.

The fifth child, Margaret S., not examined, was also a deaf-mute and was said to have a goitre.

The sixth, female, was said to be normal.

11. *The Second Bethnal Green Family.*

There was no family history of goitre or deaf-mutism. Both parents were normal. There were five children, of whom the eldest was a deaf-mute and goitrous.

James W., aged 22, a deaf-mute, first noticed a swelling of the neck at the age of 17. His thyroid was found to be considerably enlarged and irregular, and at operation Mr. Walton removed one large adenoma from the left lobe and performed a wedge-resection on the right lobe, which contained many adenomata.

The other four children were normal.

RADIUM AND THE BLOOD CHOLESTEROL¹

By CHARLES E. BRUNTON

(From the Christie Hospital and the Helen Swindells Laboratory,
Manchester University)

FROM the work of Wedd, Morson, and Russ (1), Mottram (2), Chambers (3, 4), and others, it is evident that exposure to X-rays or to radium produces a change in certain malignant tumours, such that, under a fortunate combination of circumstances, growth ceases and the irradiated cells actually produce immunity to further implants in the experimental animal. Contradictory results have been obtained as to the effect of cholesterol on tumour growths (Robertson and Burnett (5), Bulloch and Cramer (6)), and as to the blood-cholesterol content in malignant disease (Luden (7, 8); De Niord (9); Currie (10)). A flocculation reaction has been described which is diagnostic of malignant disease in a large number of cases (Fry (11)), and such reactions are not unrelated to the physico-chemical condition of the blood, which, in turn, is known to be affected by changes in the absolute and relative amounts of cholesterol present (Wells (12), Kipp (13)). The phosphatide content and the phosphatide-cholesterol ratio have been estimated in different types of normal, abnormal, and malignant tissues by Bulloch and Cramer (6), as well as by Lewis and Jowett (1926). An effect on the blood of deep X-ray therapy was found by von Babarczy (14) to be a rise in its cholesterol concentration. Observations of Roffo (15) to the effect that X-rays produce oxidation in solutions of cholesterol and inhibit or destroy its colour reactions, as well as others by Hess and Weinstock (16) and by Parsons (17), suggested the investigation of the effect of radium and of ultra-violet light on cholesterol solutions. This work has been begun. The whole question of cholesterol in the blood-serum seemed worthy of further study, and the present communication describes the beginning of such an attempt.

Five points are considered: (1) the method of cholesterol estimation, (2) the concentration of cholesterol in the blood of patients suffering from cancer, (3) its concentration in patients before and after operation under general anaesthesia for non-malignant conditions, (4) its concentration before and after diathermy for malignant disease, and (5) its concentration before and after the application of radon (radium emanation). Both the diathermy and the radium applications were given under general anaesthesia. The patients were under the care of Dr. G. E. Birkett, M.C., the Hospital Radiologist, to whom the writer is indebted

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for clinical details and information as to the dosages of radon given. Grateful acknowledgement of help must be made to the Matron and Nursing Staff of the Christie Hospital, and especially to Dr. Charles Powell White.

1. *Blood-Sampling and Cholesterol Estimation.*

Blood samples were taken by venepuncture with stasis of the basilic vein between 9 and 10.15 a.m. just before the patients' hospital 'lunch', and three hours after breakfast in the case of those patients who were not undergoing operation the same morning. Such patients had received their last meal about fifteen hours previously. In almost all the experiments the blood was withdrawn into a dry syringe; in a few the syringe had been rinsed with normal saline. From the syringe the blood was ejected into centrifuge tubes oxalated by evaporating in them 0.2 c.c. of a 10 per cent. solution of potassium oxalate, so that each tube contained about 20 mg. of oxalate. When the blood was centrifugalized in order to obtain serum, this was done within a period ranging from five minutes to two hours after venepuncture. Within these limits no change was found in the distribution of cholesterol between the corpuscles and plasma. In some cases estimations were repeated after standing the blood or serum in the ice-chest for twenty-four hours or longer.

In this investigation the estimations have been made by Myers and Wardell's method (1918), slightly modified as described below. This method does not differentiate free cholesterol from cholesterol esters. It has been studied by Gardner and Williams (18), by Whitby (19), by Campbell (20), and by others. An explanation of the colour development is given by Whitby (19).

Some encouraging results were obtained at first by Leiboff's method (1924) in spite of the *a priori* objection that traces of water are likely to remain in the final chloroform extract and prevent the development of colour with acetic anhydride and sulphuric acid. An attempt was made to overcome the difficulty by drying the filter-paper and blood at 56° C., at 70° C., and at 100° C. before putting it into the tube which is used both for extraction and colour development. The highest and best results were obtained by drying the paper for an hour at 56° C., but most of the results were lower than those obtained by Myers and Wardell's method. The results obtained on five duplicate samples are shown in Table I. The first four samples were treated according to the author's original directions. Sample 5 was treated as follows: The blood was placed on blotting-paper, and the extraction was carried out for thirty minutes in a bath at 100° C. The extraction tube and contents were then dried at 120° C. for twenty-five minutes, so that both chloroform and water might be removed. After cooling the tube in a desiccator over calcium chloride, 5 c.c. of chloroform were added and the estimation was completed in the usual way. The result in this case may be explained by a change induced in the cholesterol molecule either during the first extraction with chloroform in the presence of moisture at 100° C., or, more probably, when drying the moist chloroform extract subsequently at 120° C.

As a routine the writer heated 1 c.c. of blood or oxalated plasma with 4-5 grm. of anhydrous calcium sulphate for an hour at 100° C. Extraction was carried out for an hour on a boiling water bath in a flask containing 15 c.c. of pure chloroform. After cooling, the chloroform extract was made up to 20 c.c., and 5 c.c. portions were used for estimation with 2 c.c. of pure acetic anhydride and 0.2 c.c. of sulphuric acid. The colour was allowed to develop in a dark incubator at 30° C. for ten minutes. The reagents were supplied by the British Drug Houses. The mixing tubes were fitted with ground-glass stoppers, as chloroform will extract colour from corks. The similar difficulty which arises in the process of extraction can be overcome in the same way, or by covering the corks with tinfoil. If the latter method be used, care must be taken that the protected corks fit sufficiently closely all round to prevent loss of chloroform during extraction.

By allowing the colour to develop in the dark rather than in daylight a purer green is obtained. It cannot, however, be matched satisfactorily against a standard of naphthol green, since (1) the colour of naphthol green solutions varies on keeping, (2) different samples of the dye differ widely in the colour they give to equal quantities of water, and (3) watery solutions are to be avoided in a colorimeter cup which may inadvertently be used in a subsequent estimation for the chloroform mixture.

All those who have studied this method of cholesterol estimation have emphasized the necessity of drying and cleansing the glassware with scrupulous care. In one experiment, where tubes had been dried at 90-100° C. instead of at 110° C., a result of 141 mg. per cent. was obtained. On repetition with properly dried tubes the result was 172 mg. per cent. When all precautions were taken, the number of readings made doubtful (and therefore rejected) owing to yellowing in the final mixture for matching was about 14 per cent. of all readings made.

2. *Cholesterol in the Blood of Cancer Patients.*

In the whole blood of thirteen patients suffering from cancer the lowest concentration—115 mg. in 100 c.c.—was found in a woman who had had carcinoma of the vulva and cervix uteri for about 1½ years. The highest concentration—204 mg. in 100 c.c.—was found in a woman whose breast had been amputated three weeks previously by diathermy. The average concentration was 149 mg. in 100 c.c. of whole blood.

In forty-four oxalated plasmas the lowest concentration—97 mg. in 100 c.c.—was found in the case of a man suffering from advanced rodent ulcer of the face and orbital cavity. His general condition was poor, and he was, incidentally, one of the oldest persons examined. The highest concentration—262 mg. in 100 c.c.—was found in a woman of 62 years, who had carcinoma of the vagina. The average concentration in these plasmas was 169 mg. in 100 c.c.

The youngest patient in the series, a girl of 12 years, with a tumour in the head of the humerus, had a concentration of 131 mg. in 100 c.c. of plasma. The

oldest was a man aged 74 years, who had an advanced rodent ulcer and a plasma cholesterol of 168 mg. in 100 c.c.

The most rapidly growing tumour examined was a secondary in the ilium from a breast carcinoma which had been removed a year previously. This patient had a blood-cholesterol concentration of 238 mg. in 100 c.c. of oxalated plasma.

The number of patients examined is too small to show any relation between either the rate of growth or the age of the tumour and the blood-cholesterol concentration.

No seasonal variation was found in the cholesterol of two persons whose blood was examined in February and again in September of the same year.

Further details are given in Table II.

3. *Blood Cholesterol after Operation under General Anaesthesia.*

McAdam and Shisken (21) found a fall in the blood cholesterol after operations of all kinds whether with local or general anaesthesia. In six cases where operations under general anaesthesia were performed at the Christie Hospital for non-malignant conditions, the alterations in blood cholesterol were variable. In the first two cases the whole blood was examined, in the other four the oxalated plasma was used. All the operations were performed under open ether after an induction with open ether and chloroform mixture. All the patients made a normal recovery. The second estimations were made twenty-four hours after the operation.

A gastric ulcer was excised for a man aged 50 years. His blood cholesterol fell from 159 mg. in 100 c.c. to 114 mg. in 100 c.c.—a percentage fall of about 28 mg. in 100 c.c.

A hemithyroidectomy was performed on a man aged 26 for unilateral thyroid hypertrophy. The blood cholesterol fell from 176 to 152 mg. in 100 c.c., a percentage fall of 14 mg. in 100 c.c. In the plasma of the same patient the concentration remained unaltered.

A supravaginal hysterectomy was done for cystic ovaries and fibroids in a woman aged 40 years. The oxalated plasma cholesterol fell from 150 to 100 mg. in 100 c.c. after the operation, a percentage fall of 33.3 mg. in 100 c.c.

A dermoid cyst was removed and the uterus curetted for a woman aged 56 years. The plasma cholesterol rose from 190 to 218 mg. in 100 c.c., a percentage rise of 15 mg. in 100 c.c.

After curettage of the uterus and ligature of an anal haemorrhoid for a woman aged 60 years the cholesterol concentration of the plasma rose from 129 to 170 mg., a percentage rise of about 32 mg. in 100 c.c.

In the oxalated plasma of a man aged 37 years, for whom a gastric ulcer was excised and a gastro-duodenostomy was performed, the plasma cholesterol fell from 165 to 121 mg. in 100 c.c., a percentage fall of about 27 mg. in 100 c.c.

Thus, after six operations, there was a definite fall of cholesterol concentration in four cases and a rise in two cases. The matter seems to be worthy

of further study as regards the site of operation and the condition for which the operation is performed.

4. *Blood Cholesterol after Diathermy.*

The effect of diathermy on the blood cholesterol was noted in seven cases of rodent ulcer, one case of papilloma, and one of squamous cell carcinoma, all of the skin. To these patients no other treatment was given except chloroform as a general anaesthetic. The results showed a rise of cholesterol in three and a fall in five cases. Thus, no constant alteration occurs in the cholesterol content of the plasma after diathermy. The figures are given in Table III.

5. *Blood Cholesterol after Radiation of Malignant Growths.*

The blood cholesterol was examined in 28 cases of carcinoma and two cases of sarcoma before and after various amounts of radium emanation had been in close relationship to the tumours. The sites of these tumours included the mouth and fauces (9 cases), the tongue (6 cases), the uterus (3 cases), the rectum (3 cases), and other parts of the body. Of the 9 mouth cases, the alteration after treatment was, in 5 cases, within the limits of possible error; in 3 cases there was a definite increase, and in 1 case a definite decrease. Of 6 tongue cases, 1 result was indefinite, 2 results were increases, and 3 were decreases. There was a rise in 1 and a fall in 2 uterine cases treated. The dosage of radon varied from 5.6 millicuries for 24 hours to 141 millicuries for 72 hours, but the alterations in blood cholesterol show no relationship to the size of the dose. The estimations were done at different periods after the radon tubes had been inserted, but showed no relationship to the time which had elapsed. Fuller particulars of the radon dosages and cholesterol concentrations are given in Table IV below.

It must be admitted that the number of cases investigated is too small to serve as a basis for final conclusions on the matter. One can merely assert that no evidence was found of a constant change in the total cholesterol content of the blood as a result of tumour radiation.

Summary.

The total cholesterol content of blood and plasma, as found by Myers and Wardell's method (22), has been estimated in the case of patients suffering from cancer; in patients before and after operation under general anaesthesia for non-malignant conditions; in cancer patients before and after treatment by diathermy; and in others before and after treatment with radon.

In the whole blood of thirteen patients suffering from cancer the average concentration was 149 mg. per 100 c.c.

In the oxalated plasmas of forty-four patients the average concentration was 169 mg. per 100 c.c.

After operations for non-malignant conditions ; after treatment for malignant disease by diathermy ; and after its treatment by radon the plasma cholesterol may either increase or decrease.

In thirty patients examined before and after treatment by radon no relation was found between the alteration in cholesterol concentration and either the dose of radon or the time of its action within the limit of seventy-two hours.

TABLE I.

Sample.	Leiboff's Method (mg. in 100 c.c.).	Myers and Wardell's Method (22) (mg. in 100 c.c.).
1	97, 86, 82, 130	166, 158, 158
2	126, 98, 165, 131	151, 154
3	72, 71, 116	143, 142, 148, 139
4	105	188
5	126	156

TABLE II.

A. Concentration in Whole Blood.

No.	Sex.	Age	Cholesterol (mg. in 100 c.c.).	Type and Site of Cancer. (Ca = carcinoma. S = sarcoma.)
1	F.	57	115	Ca. vulva and cervix uteri
2	F.	12	119	Tumour head of humerus
3	M.	50	125	Ca. tongue
4	F.	51	143	Multiple large nodular recurrences ca. breast
5	M.	45	144	Ca. tongue and mouth
6	F.	57	152	Ca. breast 4 years. Fluid in abdom. cavity
7	M.	51	162	Ca. mouth
8	F.	49	169	Recurrence ca. breast. Oedema of arm
9	M.	48	169	Ca. rectum
10	M.	68	175	Ca. rectum
11	M.	59	175	Rodent ulcer of face and orbit
12	F.	47	187	Ca. breast. Recurrence in ilium
13	F.	58	204	Ca. breast. Amputation 3 weeks before by diathermy

B. Concentration in Oxalated Plasma.

1	M.	71	98	Rodent ulcer of face
2	F.	51	98	Ca. breast
3	F.	59	100	Ca. skin of arm
4	M.	43	109	Ca. skin of scrotum
5	M.	56	115	Ca. skin of cheek
6	M.	59	116	Ca. tongue and floor of mouth
7	M.	68	121	Ca. tongue
8	M.	50	127	Ca. roof of mouth
9	M.	45	130	Ca. tongue
10	F.	12	131	Tumour head of humerus
11	M.	54	131	Ca. tongue
12	M.	55	133	Ca. floor of mouth
13	M.	51	134	Ca. palate
14	F.	44	135	Ca. cervix uteri
15	M.	45	140	Rodent ulcer of cheek
16	M.	58	143	" " "
17	F.	59	144	Ca. cervix uteri "
18	F.	37	144	" " "

TABLE II (continued).

No.	Sex.	Age.	Cholesterol (mg. in 100 c.c.).	Type and Site of Cancer. (Ca. = carcinoma. S = sarcoma)
19	M.	54	145	Ca. palate and fauces
20	F.	46	151	S. thigh
21	M.	65	151	S. orbit
22	M.	69	162	Ca. mouth
23	M.	70	162	Ca. palate and fauces
24	M.	74	168	Rodent ulcer of nose and face
25	M.	61	172	Ca. floor of mouth
26	M.	67	175	Rodent ulcer of ear
27	M.	61	179	Ca. rectum
28	M.	60	180	Ca. tongue
29	M.	49	180	Ca. rectum
30	M.	70	184	S. scalp
31	F.	56	185	Ca. vagina
32	M.	70	187	S. nasal bone
33	M.	51	187	Recurrence of parotid tumour
34	M.	54	189	Ca. lip
35	M.	50	196	Ca. eyelid
36	M.	59	197	Rodent ulcer of face and orbit
37	F.	53	207	Rodent ulcer of cheek
38	F.	68	209	Ca. vulva
39	F.	50	210	Ca. cervix uteri
40	M.	52	210	Ca. skin of hand
41	F.	52	211	Ca. cervix uteri
42	F.	47	238	Ca. breast. Recurrence in ilium
43	M.	68	241	Ca. rectum
44	F.	62	262	Ca. vagina

Nos. 10, 36, 42, and 43 in section B are the same patients as Nos. 2, 11, 12, and 10 in section A of this table.

TABLE III.

Case.	Cholesterol before Diathermy (in mg. per 100 c.c.).	Cholesterol after Diathermy (in mg. per 100 c.c.).	Percentage Rise or Fall per 100 c.c.
1	175	208	+ 18 mg.
2	197	204	Change within limits of error
3	98	115	+ 17 mg.
4	140	175	+ 25 mg.
5	207	187	- 10 mg.
6	203	178	- 12.5 mg.
7	168	136	- 19 mg.
8	210	184	- 12.6 mg.
9	143	119	- 17 mg.

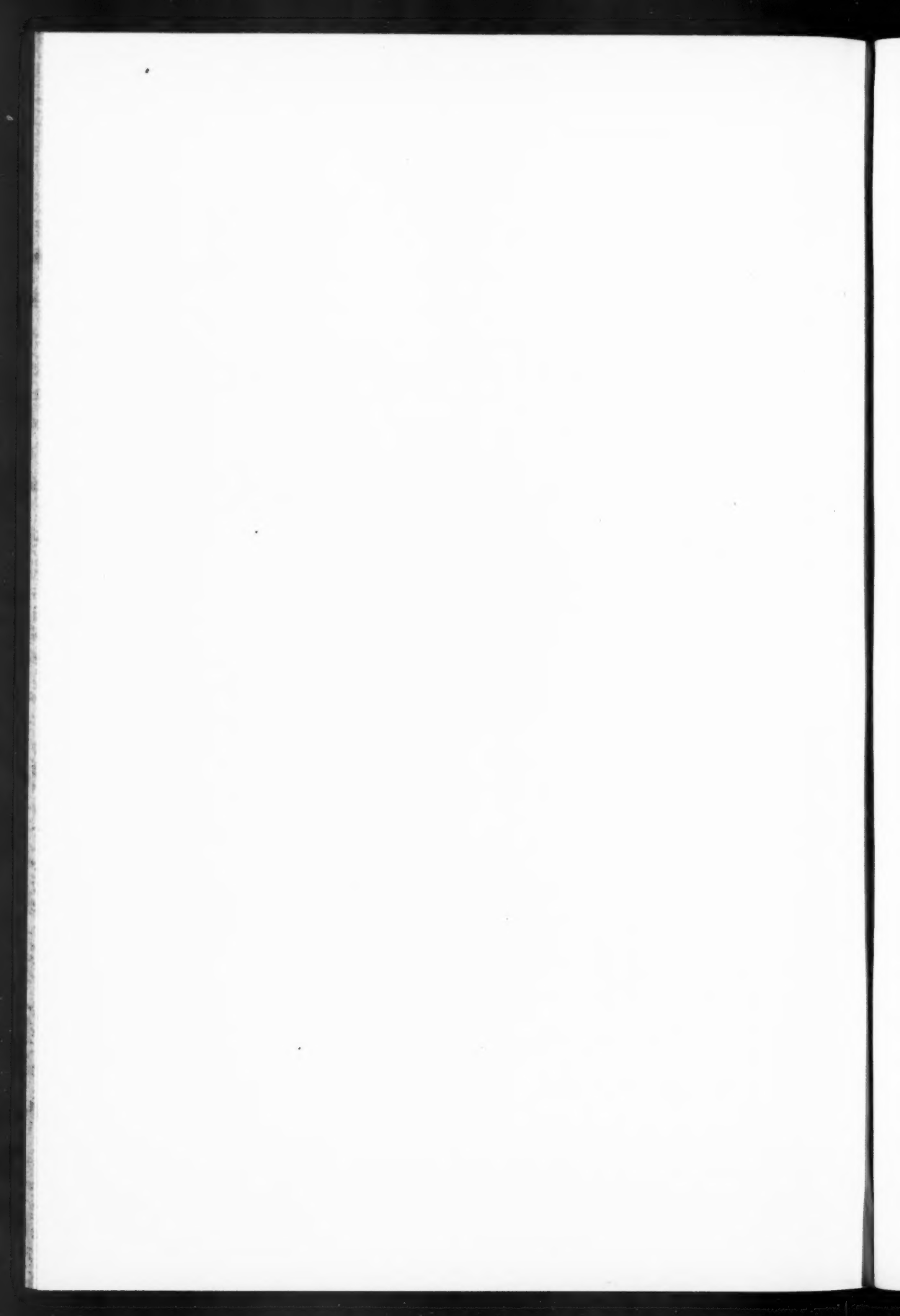
TABLE IV.

Case.	Sex.	Age.	Condition.	Radium.		Plasma Cholesterol (mg. per 100 c.c.).		Percentage Alteration (in mg. per 100 c.c.).
				Dose (in Millieuries).	Exposure (Hours).	Before Radiation.	After Radiation.	
1	M.	43	Ca. rectum. Colotomy	63	Pt. 1 24	169	177	+5
2	M.	50	Ca. tongue	66	Pt. 0.5 24	125	149	+19
3	M.	45	Ca. tongue	72	Pt. 0.5 24	143	157	+9
4	M.	56	Ca. palate	68	Pt. 0.5 24	134	151	+13
5	M.	60	Ca. tongue	64	Pt. 0.5 24	180	119	-34
6	M.	69	Ca. mouth	9.6	Nil 24	162	176	+9
7	M.	70	Ca. palate	5.6	Pt. 0.5 24	164	162	-1
8	M.	70	S. nose	5.6	Pt. 0.4 24	187	159	-15
9	M.	68	Ca. rectum	96	Pt. 0.4 24	197	204	+4
10	M.	50	Ca. roof of mouth	8	Nil 24	127	133	+5
11	M.	45	Ca. roof of mouth	44	Pt. 0.4 24	189	190	0
12	M.	61	Ca. rectum	63	Pt. 1 24	179	115	-36
13	F.	44	Ca. cervix uteri	126	{Ag. 1 } 72	135	114	-16
14	F.	59	Ca. cervix uteri	114	{Br. 0.3 } 24	144	171	+19
15	M.	54	Ca. tongue	38	Pt. {0.3 } 72	131	106	-19
16	M.	59	Ca. tongue and mouth	39	Pt. 0.4 72	116	129	+11
17	F.	37	Ca. cervix uteri	141	{Ag. 1 } 72	144	153	+6
18	M.	43	Ca. skin of scrotum	84	{Br. and Pb. } 72	109	131	+21
19	M.	54	Ca. palate and fauces	11.2	Nil 72	144	144	0
20	M.	55	Ca. floor of mouth	40	Pt. {0.4 } 72	133	106	-23
21	F.	56	Ca. vagina	112	Pt. {0.5 } 48	185	199	+8
22	M.	58	Ca. tongue and glands	42	Pt. 0.5 72	121	102	-16
23	M.	67	Rodent ulcer of ear	40	{Ag. 0.7 } 72	175	180	+3
24	M.	50	Ca. eyelid	29	Pt. 0.4 72	196	203	+4
25	M.	56	Ca. skin of cheek	42	Pt. 0.4 72	115	127	+10
26	F.	68	Ca. skin of vulva	56	Pt. 0.5 72	209	175	-16
27	F.	59	Ca. skin of arm	61	Pt. 0.4 72	100	150	+50
28	M.	61	Ca. floor of mouth	51	Pt. 0.4 24	172	182	+6
29	M.	65	S. orbit	96	Pt. 0.5 72	151	157	+4
30	M.	49	Ca. rectum	50	Pt. 0.4 72	180	168	-7

Note.—The percentage error in these estimations is estimated not to exceed 5 per cent. No percentage alteration is considered significant which does not exceed 3 mg. per 100 c.c.

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THE CLINICAL DURATION OF SACCULAR AORTIC ANEURYSM IN BRITISH-BORN SUBJECTS¹

By G. H. COLT

THE confirmatory diagnosis of saccular aortic aneurysm by screen examination is much in advance of our knowledge of the clinical duration of the disease. It will appear in the course of this paper that there are certain time factors which can be applied to an individual case which may tell us fairly accurately the probable duration of life. These results have been obtained from a collection of material which was begun in 1904 with an analysis of the fatal cases in the unpublished records of St. Bartholomew's Hospital, London, from 1871 and continued to the end of 1907, giving a series of 120 male and 10 female cases, and I am indebted to the hospital authorities for permission to use this material. Since 1908, I have had to fall back on published cases, which for the present purpose are not so valuable because the authors have generally been more concerned with the demonstration of some particular symptom or sign than with the duration of the disease. It is noteworthy that batches of such cases occur in the literature, some of which are recorded on account of their long duration. This may vitiate the conclusions, but as the total number of such long-lived cases is small and their distribution is readily seen in the tables the error is not large.

The bibliography gives the sources of all the cases, and it will be seen that almost every record of importance published in Great Britain during the last hundred years has been consulted. No case has been included unless the requisite facts were clear and reliable, and none in which there was no post-mortem examination. Also no case was included when it was not possible to obtain a definite or approximately definite history of the onset of symptoms. Cases in which an external swelling was noticed before symptoms were complained of have been regarded as unreliable and have been excluded. They come under the third heading proposed by Hewat (*Edinb. Med. Journ.*, 1917, 1. 214) of 'Aneurysms discovered accidentally'. A small number of cases in which the patient was not a British subject born of British parents has been excluded. A few cases showing tubercular lesions in the lungs have also been omitted. Cases of wiring, of wiring and electrolysis, cases treated by the injection of gelatin, the administration of acetate of lead, or by ergot, have not been reviewed

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for this paper, neither have their respective numbers been noted. Cases of dissecting and of fusiform aneurysm have been excluded except where the former were terminal events in cases of saccular aneurysm. The total number of cases excluded was 447 (391 males and 56 females), as shown in the following tables :

The number of cases excluded on account of indefinite information or other minor reasons was :

	<i>Male.</i>	<i>Female.</i>
Thoracic single	271	41
Thoracic multiple	12	3
Abdominal	35	3
	<u>318</u>	<u>47</u>

The following also were excluded :

	<i>Male.</i>	<i>Female.</i>
Cases of fusiform aneurysm	12	—
Cases of dissecting aneurysm	9	3
Cases in which the aneurysm appeared to be primarily innominate rather than aortic .	13	1
	<u>34</u>	<u>4</u>

The number of instances of exclusion on account of certain special mechanical methods of treatment having been employed was :

	<i>Male.</i>	<i>Female.</i>
Ligature	19	5
Compression	14	—
Galvano-puncture	5	—
Needling	1	—
	<u>39</u>	<u>5</u>

The possibility that the cause of the aneurysm may have been other than syphilitic may greatly influence the clinical duration of a case. No attempt, however, has been made to deal with the pathological aspect. While the site of origin has been utilized, the questions of the size of the sac and the direction of spread have been omitted. No account has been taken of the frequency of atheroma beyond the exclusion of one case of advanced disease in which a large number of pouches were found in the aorta, none of which was sufficient to warrant ascribing the death to aneurysm.

The collected cases were tabulated according to the part of the aorta from which the aneurysm arose, and the repeat cases were thus eliminated. They occur when a case is described at a meeting of a society and reported in the current medical papers. They also arise in the compilation of text-books, by quotation, and by repetition by the authors themselves. In all the accounts that have been examined there were 48 repeat cases (47 males and 1 female). Thus with the total of 447 cases excluded as shown above and the 707 cases considered valid for statistical purposes the total number of histories reviewed for the present purpose has been 1,202.

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The 707 cases thus collected consist of 130 cases with detailed records from St. Bartholomew's Hospital over the period 1871-1907, and 577 cases collected from records published during roughly the last hundred years. No attempt has been made to distinguish the time of survival in respect of cases treated at an early or late year in this long period of medical progress. It is possible that aneurysms of the aorta are now discovered earlier and treated better, at any rate by anti-syphilitic measures, than they used to be. Both factors should tend to lengthen the time of clinical duration. No correction has been made for the few instances of healed aneurysm discovered after death in old persons dying in institutions, where the aneurysm had not been known to exist during life and there was consequently no history of the clinical duration.

The Registrar-General's reports show that the average number of deaths each year from aneurysm in England and Wales over the period 1900-24 was 842 males and 206 females. In these official returns no distinction is made between aortic aneurysm and aneurysm of other arteries, but the latter appears to be very uncommon nowadays, with the possible exception of aneurysm of the popliteal artery.

The clinical duration has been counted from the first date of the longest recorded symptom, which is often quite definite in onset, until death occurred. This period has been reckoned to the nearest half-month, and where there was any doubt about this the longer of two periods has been chosen. Great care has been taken to ensure that the reckonings are accurate, especially with respect to the time spent in hospital, the months and years of record, &c. The age of the patient has been reduced to the probable age at onset within the nearest half-year. Any error which may have arisen by this process must be small and is clinically negligible. In twenty-three of the included cases the age was not recorded, and this has been allowed for throughout.

The 707 cases accepted as valid were arranged in ascending order of ages and durations both in groups and without grouping and Tables I and II prepared to give a general idea of the subject.

For the convenience of those whose time is limited the tables and graphs (Nos. 1-10) will be found particularly useful. The graphs were prepared by my friend, Mr. O. F. T. Roberts, Lecturer in Astronomy and Meteorology in the University of Aberdeen, who very kindly undertook the work of examining the statistical part of the subject. His report, which comprises the major part of the rest of this paper, is as follows:

The durations of the aneurysm for 5- or 10-year 'age of onset' groups were considered. The groups are 20-9, 30-9, &c.: years of 'age of onset' or 30-4, 35-9, 40-4, &c.: or a combination of the two, the choice depending on the number of cases, fewer cases requiring larger age subdivisions. It was apparent that:

(a) In each group there are usually several cases in which the duration is long (e.g. anything from 5 to 10 times the mean duration).

(b) The 'duration-frequency curve' is in general asymmetrical.

Summary of Cases of Saccular Aortic Aneurysm.

TABLE I. (Males.)

Group.	No. of Cases.	No. of Ages.	Situation.	Average Age (Years).	Average Duration (Months).
A. {	93 8	89 8	Ascending aorta	42-52	19-68
			Ascending aorta × ascending arch	45-37	19-56
	A. II	81	Ascending arch	43-07	20-50
B. {	35 88 29 16	35 82 29 15	Ascending × transverse arch	45-48	16-87
			Transverse arch	39-45	16-12
			'Arch'	43-03	22-39
			Transverse × descending arch	38-60	19-62
	37 14	32 14	Descending arch	43-90	13-92
			Descending arch × descending thoracic aorta	38-71	18-68
C. {	45 4	42 4	Descending thoracic aorta	40-71	22-96
			Descending thoracic × abdominal aorta	38-75	24-25
D. {	41 5 4 3	40 5 4 2	Multiple thoracic (two)	42-77	21-95
			Multiple thoracic (three)	41-20	10-20
			Multiple thoracic (four)	41-00	22-25
			Multiple thoracic (more than four)	41-00	19-00
Total	503	482	—	42-04	19-13
E.	122	121	Abdominal aorta	35-95	18-12
Total	625				

TABLE II. (Females.)

Group.	No. of Cases.	No. of Ages.	Situation.	Average Age (Years).	Average Duration (Months).
F. {	14 3	14 3	Ascending aorta	39-28	30-68
			Ascending aorta × ascending arch	48-00	15-66
	13	13	Ascending arch	41-53	39-23
G. {	6 10	6 10	Ascending × transverse arch	46-33	13-58
			Transverse arch	42-10	14-05
	4 3	4 3	'Arch'	39-5	13-625
			Transverse × descending arch	45-00	12-00
	8 4	8 4	Descending arch	33-87	12-94
			Descending arch × descending thoracic aorta	38-25	10-50
H. {	3 0	3 0	Descending thoracic aorta	35-00	30-66
			Descending thoracic × abdominal aorta		
J. {	2 2 0 0	2 2 0 0	Multiple thoracic (two)	29-00	13-75
			Multiple thoracic (three)	41-50	20-00
			Multiple thoracic (four)		
			Multiple thoracic (more than four)		
Total	72	72	—	40-22	22-27
K.	10	9	Abdominal aorta	36-70	23-65
Total	82				

In these circumstances it seemed more reasonable to employ the median and quartile method, instead of the mean and the standard deviation, because this method prevents an odd case or two of long duration from adding perhaps 10 or 20 per cent. to the average value of a group of, say, 20 cases. This method also permits the skewness of the duration frequency to be easily indicated; that is to say, it shows the usual greater scatter of the cases of long duration as compared with those of short duration. In fact the method seems to be a clear and practical way of interpreting the figures, if less sound, statistically, than taking the mean and standard deviation.

In the graphs Nos. 1-10... the abscissae are the ages of onset in years, and the ordinates the durations in months. The crosses indicate the medians of the 5- or 10-year groups, and the dots with circles round them the quartiles of the groups. When the numbers in a group are small (less than eight) the quartiles are not given; immediately above the line of zero-duration is written the number of cases in the group.

To take two concrete instances:

(1) In graph 9 we see that the number of cases between the ages of 30 and 34 of aneurysm of the whole thoracic aorta in males is 68. One quarter of these patients died in $3\frac{1}{2}$ months, another quarter died in 8 months, a third quarter in 18 months, and the rest lived longer.

(2) In graph 8 for the abdominal aorta in males there are 35 cases between the ages of 35 and 39. Of these patients one quarter were dead in 6 months, another quarter in 13 months, a third quarter in 24 months, and only a quarter of all the patients lived more than this time.

TABLE III.

Comparison of Mean Values and Medians for the cases shown in Graphs Nos. 1-10.

Graphs.	Group.	No. of Cases.	Mean Value.	Median.
1	A	182	20.00	12
2	A I	93	19.68	12
3	A II	81	20.50	12
4	B	219	17.10	10
5	B I	117	17.65	9
6	C	49	23.00	20
7	D	53	21.25	10
8	E	122	18.12	13
9	A+B+C	450	21.45	12
10	F+G+H	68	22.60	12.5

On the right-hand side of each graph are shown the medians and quartiles when the entire number of cases in the pathological division is considered as a single group of figures. Table III gives a comparison of the mean values and the medians for these groups. It shows that in every group except C the mean value is much higher than the median, as would be expected from the asymmetry of the durations.

A 'duration-frequency' graph (not published) shows a tendency for the durations to be given in round numbers in published records, i. e. it shows that in some cases an exact inquiry has not been made as to the date of onset of the disease, a point which could be largely rectified in making future records.

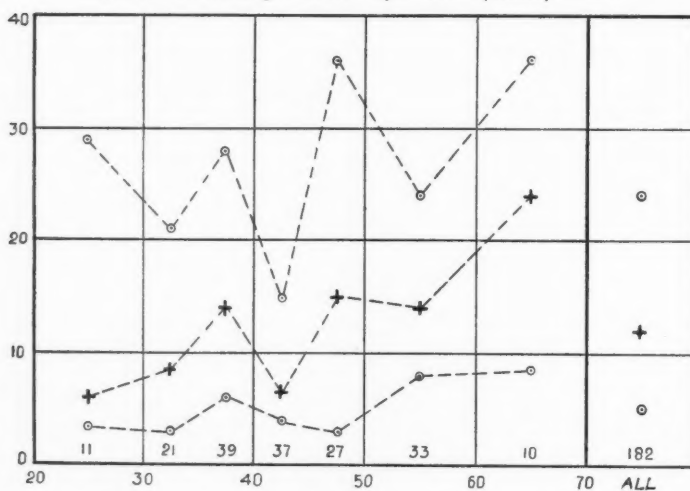
Summary.

1,202 case histories have been collected and reviewed for the purpose of determining the clinical duration of saccular aortic aneurysm. 447 of the cases have been excluded for various reasons and 48 because they were found to be duplicate cases, leaving 707 cases (625 male and 82 female) as material accepted as valid for this paper. The facts so obtained have been examined statistically by Mr. O. F. T. Roberts, who has prepared graphs and reported the results he has obtained in such a manner as to be of value for prognosis.

Remarks on the Graphs.

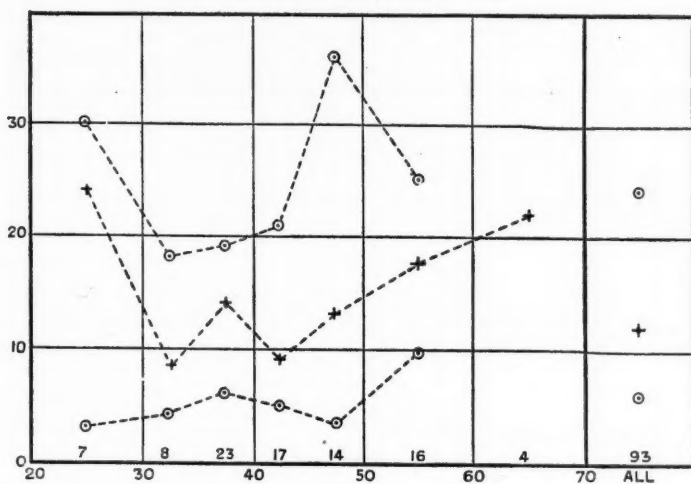
- A I. Ascending aorta (males) 93 cases, Graph 2.
 A II. Ascending arch (males) 81 " " 3.
 A. Whole ascending portion of aorta (males),
 see Table I 182 " " 1.

Whole Ascending Portion of Aorta (Males). A.

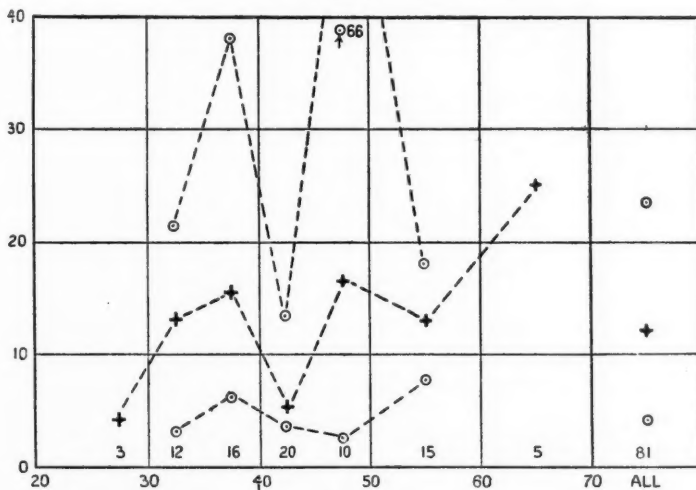


GRAPH 1.

The first two of these (A I, A II) are practically the components of the third (A). The first two have a general similarity; in particular they both indicate a marked fatality between the ages of 40 and 45. The ascending aorta patient lives somewhat

Ascending Aorta (Males). A I.

GRAPH 2

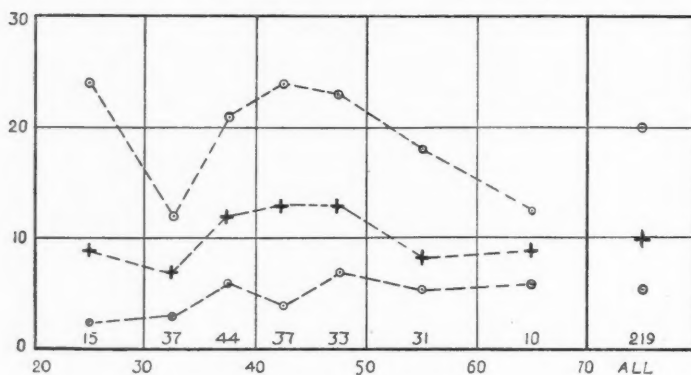
Ascending Arch (Males). A II.

GRAPH 3.

longer than the ascending arch patient at this age. Both of them, and the whole group, show a distinct increase of duration with increasing age, the expectation at 60 years of age being rather less than twice that at 35.

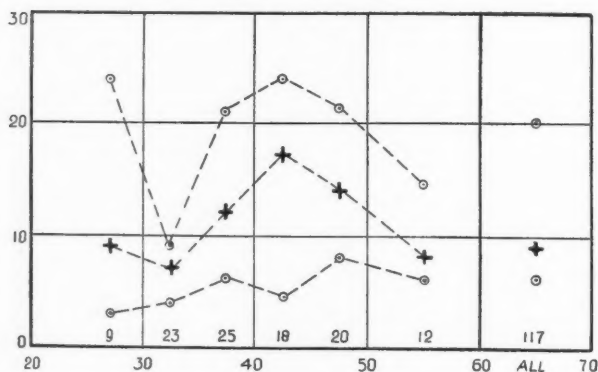
- B I. Transverse arch (males) 117 cases, Graph 5.
 B. Whole transverse portion of aorta (males)
 see Table I 219 „ „ 4.

Whole Transverse Portion of Aorta (Males). B.



GRAPH 4.

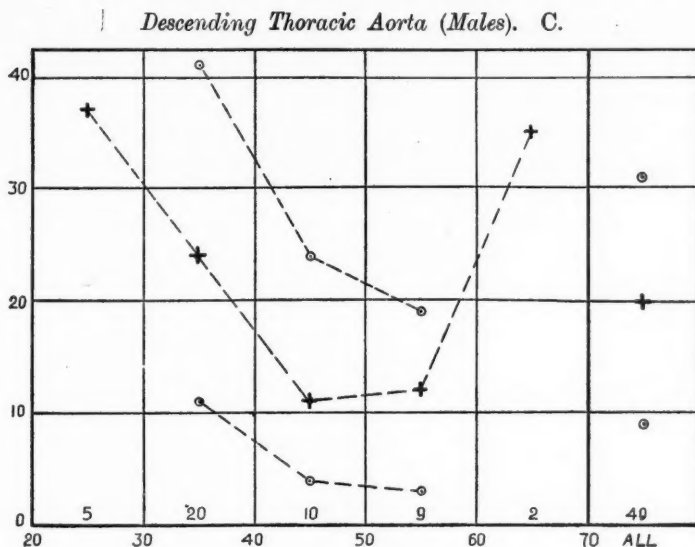
Transverse Arch (Males). B I.



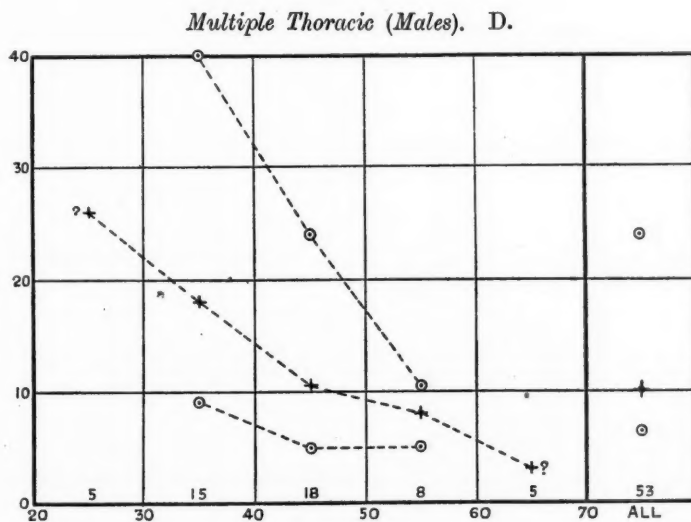
GRAPH 5.

The second (B) includes the first (B I). The curves have a general similarity; the most interesting feature is a maximum of duration between the ages of 40 and 45, occurring in both graphs; it is comparable with the minimum at the same age in the whole ascending portion of the aorta (A). Between the ages of 30 and 34 an aneurysm of the transverse portion of the arch appears to be very rapidly fatal. Apart from these points there is no particular variation of duration with age.

C. Descending thoracic aorta (males) . . . 49 cases, Graph 6.
If anything, this shows a decrease of duration with increase of age.



GRAPH 6.



GRAPH 7.

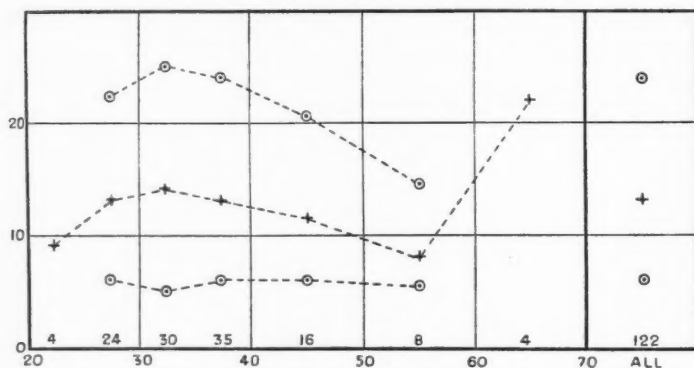
D. Multiple aneurysms of whole thoracic aorta
(males) 53 cases, Graph 7.

A striking feature is that the duration falls off rapidly with the age of onset: so that a patient of 55 has less than half the expectation of life of one of 35.

E. Abdominal aorta (males) 122 cases, Graph 8.

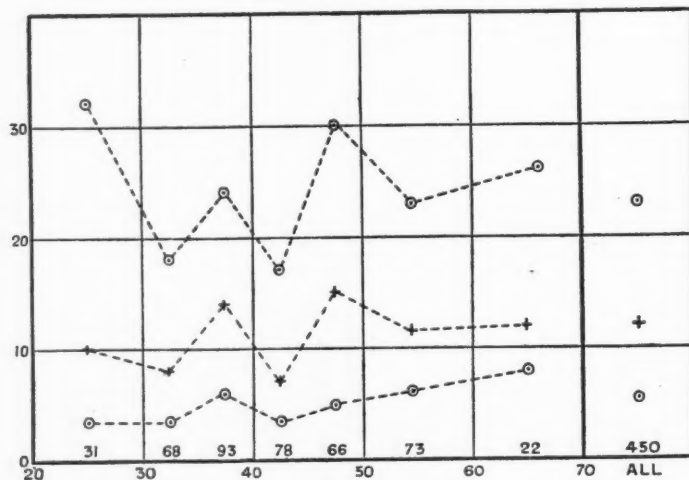
There appears to be a fall in duration from the ages of 33 to 55 years: expectation at 33 is fourteen months, at 55 eight months. Much weight, however, cannot be given to this owing to the rapid reduction of cases with age, abdominal aneurysm being, apparently, a disease chiefly affecting males from 25 to 40 years of age.

Abdominal Aorta (Males). E.



GRAPH 8.

Whole Thoracic Aorta (Males). A + B + C.



GRAPH 9.

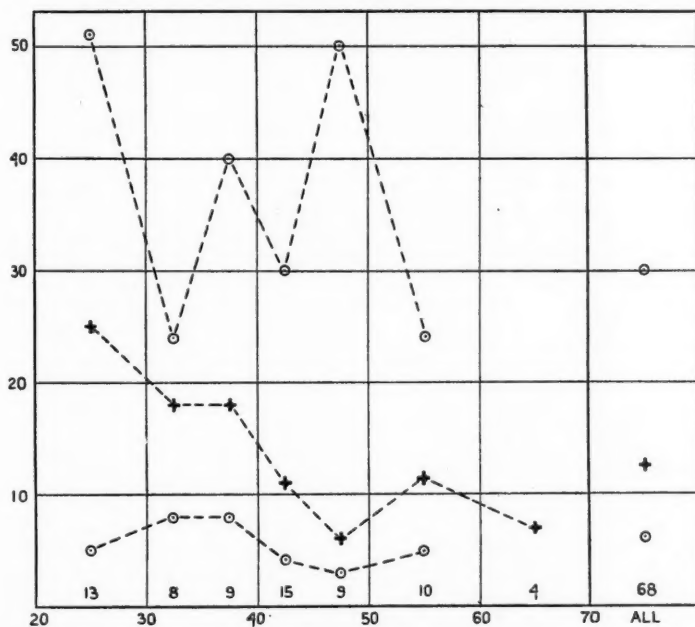
A + B + C. Whole thoracic aorta, single aneurysms
(males) 450 cases, Graph 9.

F + G + H. Whole thoracic aorta, single aneurysms
(females) 68 „ „ 10.

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In the case of the females, as far as can be judged from the small number of cases, the expectation of life falls with age; this is to be contrasted with the males, for whom in general there is little variation of this nature. There seems to be a tendency for the occurrence of isolated cases of considerable duration among the female group. A further distinction between male and female cases (Tables I and II) is that the female patient lives longer with an aneurysm of the ascending aorta than the male, whereas the male patient lives longer with an aneurysm of the transverse portion of the aorta than the female. In spite of the small number of observations (65) in the female groups, these distinctions appear in each subdivision except that of ascending aorta \times ascending arch.

Whole Thoracic Aorta (Females). F + G + H.



GRAPH 10.

In males, for the three chief sections of the thoracic aorta, as indicated by the graphs 1, 4, and 6, the order of ascending duration is B (transverse), A (ascending), and C (descending thoracic). C refers to only 49 cases, whereas B and A refer to 219 and 182 respectively. The longer duration in C, however, compared with the other two, is well marked.

Mr. Roberts's conclusions will be of value as a basis on which to found the prognosis as regards the mere duration of life. The only other considerations of this subject found in the bibliography are as follows:

Welch (*Trans. Roy. Med. Chi. Soc., Lond., 1876, 59*) considers 34 cases in soldiers. Habershon (*Guy's Hosp. Reports, 1863, S. 3, 9, p. 75*) considers the clinical duration of aneurysm of the abdominal aorta, and gives two years as an

ordinary limit; Bryant (*Clinical Journ.*, 1903) gives the average as 13 months in 54 cases; and Nunneley (loc. cit.) 15 months in 26 cases. Sir Thomas Oliver (*The Lancet*, 1909, i. 971), F. de Havilland Hall (loc. cit.), and Osler (loc. cit.), consider the question in general. The figures given by F. de Havilland Hall in 27 cases in private practice are some 50 per cent. better than the average in the present collection; he would consider three years as near the mark in such cases. Brockbank (*Medical Chron.*, April and May, 1909) gives the average age from the post-mortem records of the past 40 years at the Manchester Royal Infirmary, of aneurysm of the aorta, in 136 males as 42.1 years, and in 21 females as 44.6 years, and from Crisp's tables (loc. cit.) we find the average age in 155 male thoracic cases to be 39.75 years, and in 33 female cases 45 years. In 36 male abdominal cases the average age is given as 32.30 years. Crisp's cases were before the year 1847. Byrom Bramwell's conclusions (loc. cit.) and Lee Dickinson's (*Trans. Path. Soc.*, Lond., vol. 49, p. 50) do not differ materially from those indicated in this paper.

My former house-surgeon, Dr. R. J. Duthie, made himself responsible for the extracts from eighty years of *The Lancet*. To him and to numerous friends who have helped with the preliminary arrangement of the figures and other clerical work, and to many registrars of hospitals and others who have taken great pains to trace some of the long-continued cases, I wish to offer my grateful acknowledgement.

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² This series, which contains much relevant material, was not available to me. Should it be utilized by any one I should be glad to point out any possible repeat cases.—G. H. C.

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*Cases of Saccular Aortic Aneurysm.**Ages arranged in Ascending Order (in Sections).*

The ages have been reduced to the age of the patient in years at the onset of the disease, and are probably correct to the nearest half-year. The durations are given in months, and with possibly a very few exceptions are correct to the nearest half-month.

MALES.

Ascending Aorta (93 Cases).

Age.	Durn.	Age.	Durn.	Age.	Durn.	Age.	Durn.	Age.	Durn.
21	31	35	18	40	4	46	1	54	24
24	4	35	21	40	19	46	36	54	180
24	75	36	6	40	25	46	36	55	$7\frac{1}{2}$
25	3	36	14	40	41	48	3	56	7
26	$2\frac{1}{2}$	36	48	41	2	48	9	57	9
26	26	37	8	41	13	48	14	57	10
28	24	37	10	42	4	48	26	57	$62\frac{1}{2}$
30	12	37	14	42	7	48	36	58	8
31	$23\frac{1}{2}$	37	72	42	$24\frac{1}{2}$	49	2	59	10
31	50	38	$1\frac{1}{2}$	42	90	49	$3\frac{1}{2}$	62	$8\frac{1}{2}$
32	$8\frac{1}{2}$	38	$5\frac{1}{2}$	43	$1\frac{1}{2}$	49	12	62	36
32	$8\frac{1}{2}$	38	10	43	6	49	$49\frac{1}{2}$	66	6
33	$\frac{1}{2}$	38	19	43	13	50	25	69	36
33	7	38	30	44	$6\frac{1}{2}$	50	24	—	22
34	1	38	75	44	7	51	$11\frac{1}{2}$	—	21
35	1	39	13	44	9	51	$24\frac{1}{2}$	—	4
35	6	39	14	44	9	51	49	—	12
35	6	39	14	45	$5\frac{1}{2}$	52	24		
35	7	39	18	45	24	54	10		

Ascending Aorta × Ascending Arch (8 Cases).

Age.	Durn.	Age.	Durn.	Age.	Durn.	Age.	Durn.	Age.	Durn.
25	73	45	$2\frac{1}{2}$	47	15	55	16	63	5
30	5	46	34	52	6				

Ascending Arch (81 Cases).

Age.	Durn.	Age.	Durn.	Age.	Durn.	Age.	Durn.	Age.	Durn.
28	$2\frac{1}{2}$	35	8	40	$4\frac{1}{2}$	44	$1\frac{1}{2}$	51	73
28	6	35	41	40	$6\frac{1}{2}$	44	4	52	18
29	4	35	50	40	7	46	5	52	25
31	3	36	$7\frac{1}{2}$	40	12	46	72	53	13
32	$2\frac{1}{2}$	36	13	41	5	47	2	53	15
32	12	37	6	42	1	48	$\frac{1}{2}$	55	3
33	2	38	5	42	3	48	20	55	7
33	$2\frac{1}{2}$	38	$6\frac{1}{2}$	42	4	48	66	55	14
33	3	38	18	42	4	48	156	55	18
33	14	38	21	42	16	49	$2\frac{1}{2}$	56	11
33	16	38	35	42	26	49	15	59	5
34	14	38	41	42	38	49	18	60	25
34	27	39	35	43	$1\frac{1}{2}$	50	2	61	41
34	48	39	150	43	5	50	$8\frac{1}{2}$	62	18
34	120	40	2	43	15	50	12	62	23
35	$2\frac{1}{2}$	40	4	43	24	51	16	63	52
35	4								

Ascending Arch × Transverse Arch (35 Cases).

Age.	Durn.	Age.	Durn.	Age.	Durn.	Age.	Durn.	Age.	Durn.
22	49	38	6	42	180	46	5	56	$1\frac{1}{2}$
30	$2\frac{1}{2}$	40	1	43	7	49	15	56	16
30	12	40	12	44	13	53	$1\frac{1}{2}$	58	2
32	2	40	15	44	14	54	3	60	8
33	12	40	24	44	21	54	4	60	13
35	12	41	$3\frac{1}{2}$	45	9	54	$11\frac{1}{2}$	66	6
35	21	41	10	45	64	55	12	67	2

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Transverse Arch (88 Cases).

Age.	Durn.	Age.	Durn.	Age.	Durn.	Age.	Durn.	Age.	Durn.
24	120	33	6	38	37	43	18	50	2
26	32	33	6½	38	61	43	18	50	8
27	3½	33	8	38	72	43	36	52	8
28	2	34	7	39	4½	43	49	52	10
29	2	34	8	39	12½	44	27	52	19
29	9	34	12½	39	15	45	2	54	9
30	3	35	½	39	16	45	5	54	49
30	7	35	6	39	23	45	7½	55	16
30	8	35	16	39	31	45	13	58	3
31	1	36	6	40	1½	45	24	58	7
31	2	36	7	40	3	46	6	61	12½
31	5	36	8	40	4½	46	16	—	37½
31	6	37	3½	40	16	47	8½	—	4
31	36	37	6	40	18	47	19	—	15
32	1	37	36	41	1	49	16	—	24
32	3	38	6	42	24	49	11	—	8½
32	12	38	8	43	7½	49	12	—	29
32	96	38	12	43	12				

'Arch' (29 Cases).

Age.	Durn.	Age.	Durn.	Age.	Durn.	Age.	Durn.	Age.	Durn.
26	8	33	3	41	24	45	60	56	6
29	9	35	20	42	16	45	73	58	7
29	10	36	5	43	10	45	132	59	6
30	9	37	3	43	63	48	13	67	8
30	26	39	18	45	15	49	7	68	6
31	3	40	½	45	36	54	43		

Transverse Arch × Descending Arch (16 Cases).

Age.	Durn.	Age.	Durn.	Age.	Durn.	Age.	Durn.	Age.	Durn.
28	2	35	18	36	47½	40	5	55	55
29	12	36	7	37	24	42	3	57	36
32	5½	36	20½	38	29	45	23	—	24
33	2½								

Descending Arch (37 Cases).

Age.	Durn.	Age.	Durn.	Age.	Durn.	Age.	Durn.	Age.	Durn.
28	½	35	5	43	39	52	26	60	12
29	9	37	24	46	27	53	5½	66	24
31	½	38	3	46	36	53	31	—	12
31	26	38	4	48	4	55	8½	—	2
33	4	38	9	49	3	56	22	—	2½
34	6	40	4½	49	15	57	7	—	10
34	7	42	½	51	15½	57	11½	—	10
34	7½	42	81						

Descending Arch × Descending Thoracic Aorta (14 Cases).

Age.	Durn.	Age.	Durn.	Age.	Durn.	Age.	Durn.	Age.	Durn.
29	28	35	1½	37	6	41	2	48	3½
30	24	35	29	39	16	45	9	51	6
30	120	36	8	40	7½	46	1		

Descending Thoracic Aorta (45 Cases).

Age.	Durn.	Age.	Durn.	Age.	Durn.	Age.	Durn.	Age.	Durn.
25	39	32	3½	37	10	44	10	55	3½
27	48	33	2	37	24	44	12	56	3
28	16	33	12	38	24	45	9	58	2½
29	37	33	12	39	42	46	24	58	16
30	36	33	13	39	120	50	16	61	43
30	41½	34	7	40	2	52	24	63	22
31	1½	34	24	40	24	52	36	—	38
31	42	35	49	41	4	53	12	—	9
31	72	36	32	42	1	55	2	—	8

MALES.

Cases of Saccular Aortic Aneurysm (continued).

Descending Thoracic x Abdominal (4 Cases).

Age.	Durn.	Age.	Durn.	Age.	Durn.	Age.	Durn.
27	18	36	12	45	31	47	36

Multiple Thoracic Two (41 Cases).

Age.	Durn.	Age.	Durn.	Age.	Durn.	Age.	Durn.	Age.	Durn.
21	30½	35	81	40	3½	45	8	54	6
25	36	36	42	40	11	46	28	55	3½
28	6	37	8	40	18	48	32	58	8
29	36	38	26½	40	25	49	4	60	½
31	4½	39	43	42	5	52	7½	60	8
34	9	39	216	42	15	52	10	60	9
34	36	40	2½	42	24	53	4	61	3
35	8½	40	3	43	10	53	11	—	48
35	9½								

Multiple Thoracic Three (5 Cases).

Age.	Durn.	Age.	Durn.	Age.	Durn.	Age.	Durn.	Age.	Durn.
29	6½	30	10	39	10	42	24	66	½

Multiple Thoracic Four (4 Cases).

Age.	Durn.	Age.	Durn.	Age.	Durn.	Age.	Durn.
34	18	34	26	43	6	53	9

Multiple Thoracic more than Four (3 Cases).

Age.	Durn.	Age.	Durn.	Age.	Durn.
41	9	41	24	—	24

Abdominal Aorta (122 Cases).

Age.	Durn.	Age.	Durn.	Age.	Durn.	Age.	Durn.	Age.	Durn.
19	49	28	36	32	14	36	30	42	3½
22	4	29	11	32	14	36	36	43	82½
23	13	29	14	32	18	36	24	44	5
23	17	29	16	32	25	37	7	45	6
24	5½	29	24	32	36	37	12	45	20
25	13	30	1½	33	2	37	24	46	6
25	13	30	4	33	10	37	35	46	7
25	17	30	5½	33	11	38	3½	46	8
25	24	30	6	33	25	38	6	46	45
26	10	30	9	34	4	38	12	48	9
26	12	30	15	35	1	38	18	48	21
26	16	30	17	35	4	38	20	50	8
26	36	30	19	35	5½	38	24	50	24
26	100	30	24½	35	6	38	25	51	6
27	3½	30	25	35	6	38	48	51	8
27	3½	30	48	35	6	38	96½	52	2
27	13	30	108	35	6	39	6	52	9
27	37	31	4	35	8	39	12	56	5
28	4	31	18	35	12	39	14	57	20
28	4½	31	24	35	12	39	30	64	18
28	5	31	54	35	13	40	6	72	3
28	6	32	1½	35	24	41	14	75	26
28	6	32	1½	35	29	41	14	85	48
28	14	32	12½	36	13½	42	22	—	18
28	21	32	12½						

FEMALES.

Ascending Aorta (14 Cases).

Age.	Durn.	Age.	Durn.	Age.	Durn.	Age.	Durn.	Age.	Durn.
23	49	26	12½	39	10	50	13	54	12
25	43	28	79	41	36	50	24	67	6
26	4	28	120	42	13	51	3		

Ascending Aorta × Ascending Arch (3 Cases).

Age.	Durn.	Age.	Durn.	Age.	Durn.
46	1	48	38	50	8

Ascending Arch (13 Cases).

Age.	Durn.	Age.	Durn.	Age.	Durn.	Age.	Durn.	Age.	Durn.
29	42	37	12	42	34	46	6	48	17
30	24	41	20	42	136	47	84	58	11
36	60	41	54	43	10				

Ascending Arch × Transverse Arch (6 Cases).

Age.	Durn.	Age.	Durn.	Age.	Durn.	Age.	Durn.	Age.	Durn.
34	2	40	6	49	4	58	24	60	7½
37	38								

Transverse Arch (10 Cases).

Age.	Durn.	Age.	Durn.	Age.	Durn.	Age.	Durn.	Age.	Durn.
29	6½	36	60	43	11	44	2½	51	36
33	6½	38	2	43	12	49	2	55	2

'Arch' (4 Cases).

Age.	Durn.	Age.	Durn.	Age.	Durn.	Age.	Durn.
30	23	38	24	40	1½	50	6

Transverse Arch × Descending Arch (3 Cases).

Age.	Durn.	Age.	Durn.	Age.	Durn.
22	25	48	2	65	9

Descending Arch (8 Cases).

Age.	Durn.	Age.	Durn.	Age.	Durn.	Age.	Durn.
17	1½	28	57	34	11	44	3
22	1	31	24	35	2	60	4

Descending Arch × Descending Thoracic Aorta (4 Cases).

Age.	Durn.	Age.	Durn.	Age.	Durn.	Age.	Durn.
32	12	35	18	40	6	46	6

Descending Thoracic Aorta (3 Cases).

Age.	Durn.	Age.	Durn.	Age.	Durn.
23	8	34	24	48	60

FEMALES.

Cases of Saccular Aortic Aneurysm (continued).

Multiple Thoracic Two (2 Cases).

Age.	Durn.	Age.	Durn.
21	24	37	3½

Multiple Thoracic Three (2 Cases).

Age.	Durn.	Age.	Durn.
34	25	49	15

Abdominal Aorta (10 Cases).

Age.	Durn.	Age.	Durn.	Age.	Durn.	Age.	Durn.	Age.	Durn.
30	24	32	27	35	8	42	14	45	9
32	5½	34	5	37	7	44	5	—	132

THE EFFECT OF ADMINISTRATION OF PARATHYROID ON THE SERUM CALCIUM¹

BY C. P. STEWART AND G. H. PERCIVAL

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Department for Diseases of the Skin, Royal Infirmary, Edinburgh)

IN the April 1926 issue of this Journal we published an account of observations on the serum calcium in various pathological conditions. Amongst other things we noted that in certain cases administration of parathyroid gland was followed by an increase in the serum calcium, although prior to that administration the level had remained constant for some time. This effect, however, was not always manifested, and it was suggested that the difference lay in the initial value of the serum calcium: that when it was normal or only slightly below that level, parathyroid did definitely bring about a rise, but that when it had been subnormal for some time, there was no change.

In the present communication we submit the results of some further experiments on the same lines, in which we have confined our attention to eleven subjects,² whose serum calcium was originally normal or slightly above normal. In each case the serum calcium was estimated at frequent intervals for a period of ten to fourteen days immediately before administration of parathyroid (Martindale) was commenced. In every case the serum calcium remained steady during this preliminary period. In every case the administration of parathyroid was followed by a rise in the serum calcium. The curves obtained in three absolutely typical cases are shown in Fig. 1.

By various means it has been shown that only some 60 per cent. of the serum calcium is readily diffusible, and Vines (1) suggests that there is some evidence for the view that the parathyroid glands normally aid in preserving the equilibrium between the readily diffusible and the 'bound' calcium. Curves given by him (2) show that when the total serum calcium is raised by injection of calcium chloride or parathyroid, the diffusible calcium is raised not only absolutely but also relatively to the total. On the other hand, the evidence derived from the study of tetania parathyreopriva is conflicting. Moritz (3), Salvesen and Linder (4), and Trendelenburg (5) find that the lowered total serum

¹ Received December 3, 1926.

² Six cases of psoriasis, one case of leg ulcer, one of pustular acne, two of erythema perstans, and one of dermatitis traumatica.

[Q. J. M., April, 1927.]

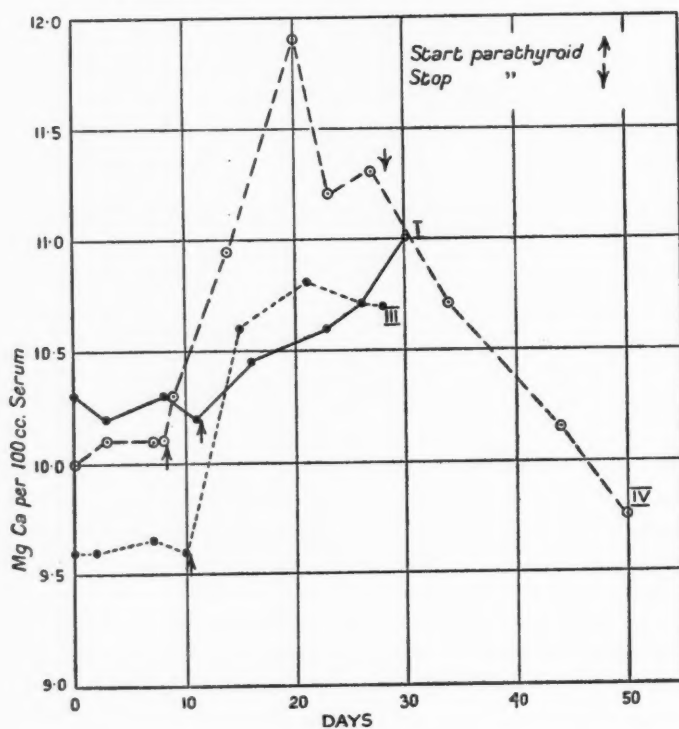


FIG. 1.

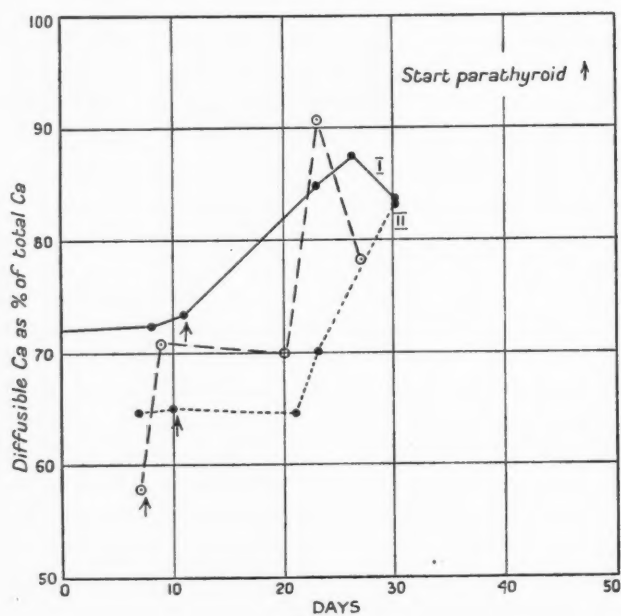


FIG. 2

calcium of tetany is accompanied by a relatively lowered diffusible calcium; Meysenberg and McCann (6) find the ratio to be unaltered; and Cruickshank (7) finds the diffusible calcium to show a relatively less fall than the total. Further, Moritz (3) states that after administration of parathyroid the diffusible and total serum calcium rise so that the ratio remains unaltered.

The methods available for the determination of the so-called ionized, active, or diffusible portion of the serum calcium are far from being satisfactory. Vines (1) has elaborated a technique in which he adds to the serum an amount of ammonium oxalate equivalent to the total calcium present. He considers that under these circumstances the ionic calcium alone is precipitated, whereas the addition of a considerable excess of oxalate is necessary to bring about complete precipitation of the remainder. The difficulty of adding an exact equivalent of ammonium oxalate, the disturbance of the equilibrium between the ionized and un-ionized calcium, as well as the time factor, all conspire to make this method unreliable. Other methods are those of dialysis of the serum against a solution of known calcium concentration (8) or distilled water (9), and of filtration through a collodion membrane (10), all of which are slow, and for various reasons, such as those already stated, cannot be expected to yield accurate results. In the latter methods it is of course the readily diffusible calcium which is measured, and since electrometric determinations (11) show that the serum contains only 1-2 mg. per 100 c.c. of calcium ion, a clear differentiation between the two states is essential for the correct interpretation of results.

We thought it might be worth while to carry out estimations of the diffusible calcium at the same time as of total serum calcium, and for this purpose we employed the method of collodion filtration. We at once found very great variations from day to day in spite of the use of carefully standardized collodion tubes. Investigation of these variations showed in the first place that a preliminary drying of the collodion membrane was essential to avoid variable dilution of the filtrate, for with the small quantities of serum necessarily employed, variation in the water-content of the membrane became important. The effect of first submitting the membrane to filtration under a pressure of one and a half atmospheres for one hour before the serum was added is shown in the subjoined table:

<i>Time of Filtration.</i>	<i>Mg. Ca/100 c.c. Filtrate.*</i>
A. (Membrane surface dried by filter-paper.)	
0 - 3 hours	4.4
3 - 7 "	7.4
7 - 22 "	8.5
B. (Membrane under pressure 1 hour before commencement of filtration.)	
0 - 1½ hours	7.45
1½ - 7 "	7.60
7 - 24 "	8.70

* Whole serum: 9.1 mg. Ca/100 c.c.

where the 7.4 value is obviously the more correct. Secondly, it appeared that the time allowed for filtration, though in no case was a biuret-free filtrate

obtained, was important. The table shows that with preliminary drying of the membrane a filtrate containing a constant amount of calcium was obtained so long as the time of filtration did not exceed seven hours. Thereafter the filtrate contained a greater concentration of calcium. No doubt this is due to a disturbance of the equilibrium between the different forms of combination of calcium in the serum.

With suitable precautions, the preliminary drying of the collodion membrane and the standardization of the time of filtration to seven hours, we obtained results (shown in Curve II, Fig. 2) which are in agreement with the statement that an increase in the serum calcium, at any rate, when brought about by parathyroid administration, is accompanied by an absolute and relative increase of the diffusible calcium.

We may perhaps be permitted a short note at this point. Case V of our series suffered for two years from extensive varicose ulceration of both legs. It is worthy of note, in view of the present-day opinion concerning the aetiological importance of the serum calcium, and the results of calcium therapy, in this disease, that the initial value of the serum calcium was normal, and also that, in spite of a very definite increase of this level following the commencement of parathyroid administration, no coincident improvement in the condition was observed.

Our thanks are due to Dr. F. Gardiner and Dr. R. Cranston Low, who placed the necessary cases at our disposal.

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INTRACRANIAL HAEMORRHAGE IN INFANCY AND CHILDHOOD¹

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With Plates 4 and 5

ALTHOUGH much has been written upon the subject of intracranial haemorrhages in the newborn, and more especially those haemorrhages produced during and immediately after the process of labour either by trauma to the skull and its contents, or by asphyxia, less attention seems to have been paid to those intracranial haemorrhages occurring from other causes in infancy and childhood. This is probably due in part to the relative infrequency of haemorrhages other than those occurring in the newborn.

The purpose of the present investigation is chiefly to inquire into the frequency and causation of intracranial haemorrhage in children past the neonatal period. I shall only refer incidentally to haemorrhage in the newborn, and the various factors which may be concerned in the production of such haemorrhages, such as the presentation of the child, the duration of the labour, the use of forceps or other forms of manipulation, will not be dealt with, as it is not the purpose of this article to review the work already done upon intracranial birth trauma.

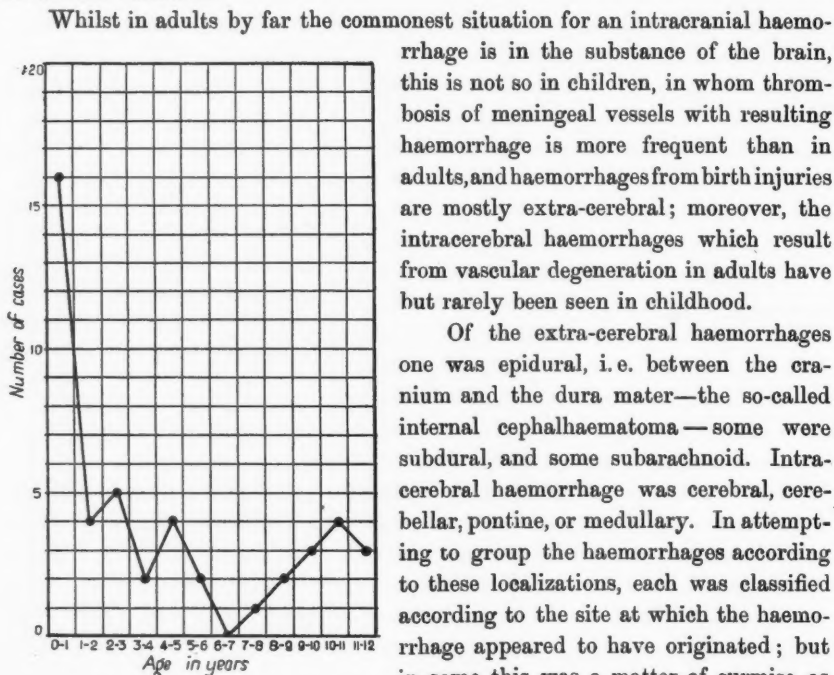
In examining the post-mortem records of the Hospital for Sick Children, Great Ormond Street, since 1860, a few of the cases catalogued under the title of cerebral haemorrhage have not been included in the series, because the haemorrhages in these seemed to be nothing more than unusually well-marked *puncta cruenta* occurring as part of the cerebral congestion which is common in death following convulsive states. Only those cases in which there was actual extravasation of blood sufficient to be unmistakable have been included.

An analysis of 10,150 consecutive post-mortem examinations showed exactly fifty cases of intracranial haemorrhage in children under 12 years of age, giving a percentage of just under 0.5. The condition is therefore uncommon at necropsy. Its relative infrequency is seen by comparison with some other fatal cerebral affections. In 1,300 post-mortem examinations at the Children's Hospital, tuberculous meningitis was found in 11 per cent., and cerebral tumour in 2 per cent.

¹ Received December 14, 1926.

There appears to be no special sex incidence. Of fifty cases (including four cases of labour haemorrhage) twenty-six occurred in boys, twenty-four in girls.

Even if those due to labour are excluded, intracranial haemorrhage appears to be much more common in the first year of life than later. The following chart, showing the number of cases in each year of life up to twelve years, illustrates this point. After the first twelve months, the figures for the succeeding years show little variation.



the haemorrhage was not confined to one group.

Of the 50 cases, 28 were extra-cerebral, 22 intracerebral. The following table shows their more exact distribution :

Epidural	1
Subdural	11
Subarachnoid	16
Cerebral	16
Cerebellar	4
Pontine and medullary	2

It will be observed that these figures bear out the previous statement that the intracranial haemorrhages of children differ from those of adults in that the majority occur in the meninges rather than in the brain.

These various haemorrhages will be considered here in the order of their occurrence: (1) before birth, (2) during or immediately after birth, (3) those

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of later date. The fifty cases in the order in which they appear in the text are summarized in the following table :

Disease.	No. of Cases.	Age.	Position of Haemorrhage.
Intracranial trauma during labour	4	1-28 days	{ 1 Epidural 2 Subdural
Probably produced at birth	1	3 months	{ 1 Cerebral (temporal lobe) Remains of cerebral haemorrhage
Congenital syphilis	1	3 weeks	Subarachnoid
Icterus neonatorum	2	3-6 weeks	Subdural
Trauma	3	{ 21 months 3 years 7 years	{ Subdural Medullary Cerebral (centrum ovale)
Associated with lumbar and ventricular puncture	2	5 months	Subarachnoid
Chronic nephritis	1	12 years	Cerebral (occipital lobe)
Acute lymphoid leukaemia	1	3 years	Subdural
Splenic anaemia of infants	1	1 year	Subdural
Purpura haemorrhagica	3	3-5 years	{ 2 Subdural 1 Cerebellar
'Anaemia'	2	4 years	Cerebellar
Lymphadenoma	1	10 years	Subdural
Whooping-cough	1	2 years	Subarachnoid
Varicella	1	5 years	Subdural
Malignant endocarditis	7	8-11 years	Cerebral hemispheres (brain unopened in one case)
Congenital heart disease with malignant endocarditis	1	10 months	Cerebral
Hypertrophic pyloric stenosis	1	9 weeks	Subarachnoid
Cleft palate	2	2-4 weeks	{ Subarachnoid Cerebral
Tuberculous peritonitis	2	{ 2 years 9 years	{ Pontine Cerebellar
Tuberculous pleurisy	1	2 years	Cerebral
Acute suppurative arthritis	1	4 years	Cerebral
Pneumonia	3	4-11 months	Subarachnoid
Empyema	2	2-12 months	Subarachnoid
Septic meningitis	1	2 months	Subarachnoid
Tuberculous meningitis	3	3 months-4 years	{ 2 Subarachnoid 1 Cerebral (frontal lobe)
Diabetes mellitus	1	11 years	Subarachnoid
Pseudo-hypertrophic muscular paralysis	1	8 years	Subarachnoid

None of our cases were prenatal, but there are such on record. Gibb (1), in 1858, recorded the case of a child who succumbed during the process of a difficult labour, and was found to have a left-sided hemiplegia, the contractures of the limbs on the left side being so rigid that, without breaking tendons, the joints could not be extended. When the brain was examined, there was found in the right hemisphere above the ventricle the remains of an old blood-clot. Three months before the child was born, the mother had received a severe blow on the abdomen by a plank of wood. The case throws some light on the pathogenesis of congenital infantile cerebral palsies.

A second instance of prenatal haemorrhage was reported by Osler (2); a woman, the subject of congenital syphilis, died, when six months pregnant, of typhoid fever. After death, the foetus was removed from the uterus, and in the left cerebral hemisphere, occupying most of the centrum ovale, was a ragged

cavity containing a large recent blood-clot, which had ruptured into the lateral ventricle. Had the mother recovered, this infant would almost certainly have suffered from some form of cerebral palsy.

Von Reuss (3) quotes two further cases; one was recorded by Seitz in a macerated mature foetus, the other was found in an infant delivered by Caesarean section before the onset of labour (Kustner).

Haemorrhages produced during or immediately after Birth.

Of those haemorrhages which are found soon after birth, within the first fortnight of life, practically all are the result of labour, although not necessarily produced by actual trauma to the brain or its meninges, for in some cases in which labour has been relatively easy the infant has been born severely asphyxiated, to a degree sufficient to produce haemorrhage. In other cases there seems little to account for the haemorrhage. East (4) recorded an extensive subdural haemorrhage in an infant one day old; the birth of the child had been normal, and at autopsy no evidence of injury was found. There were, however, small purpuric patches in the skin, lungs, and heart, and the haemorrhages were regarded as due to changes either in the blood or capillary walls. In connexion with this view of the case, it has been shown by Rodda (5) and others that in the so-called haemorrhagic diathesis of the newborn, the coagulation time of the blood is prolonged, and it may be that in such circumstances, if the degree of violence during birth is sufficient to start a haemorrhage, this may easily continue long enough to cause serious results.

Four of our cases were the result of birth injury. All died within the first month, and in all the birth had been difficult and prolonged, and forceps had been used to aid delivery. In three the haemorrhage was confined to the meninges in the middle and posterior fossae, but in the fourth, not only were large clots found over the right temporal lobe, filling the anterior part of the middle fossa, but the whole of the right temporal lobe was destroyed by a haemorrhage which had ploughed up its substance.

It seems likely that the situation of the haemorrhage has some bearing upon the prognosis in these cases, for McNutt (6) found that those in which the haemorrhage was limited to the convexity of the brain either had no convulsions, or else convulsions limited to part of the body, and also tended to have a longer duration of life; whereas those with haemorrhage at the base of the brain had convulsions of no localizing significance, and died soon after birth. The same author was able to show that haemorrhages at the convexity were generally associated with a breech presentation.

The symptoms produced by such haemorrhages may be few. Convulsions are common, but may not begin until after the first week. The child often seems quite unable to suck or to cry, and the anterior fontanelle may be tense, bulging, and without the normal pulsation. Symptoms, however, may be absent. Thus a male child, aged 2 hours, was brought to the Hospital for Sick Children for

a fracture of the left femur produced during labour. After thirty-six hours he died suddenly, and nothing had been noticed to suggest injuries other than that to the femur. Nevertheless, at the necropsy the occipital bone was found fractured from side to side across its widest portion, and there was a haematoma weighing 85 grm. beneath the dura mater in the posterior fossa of the skull.

Evidence of recovery in these cases is sometimes furnished at a subsequent post-mortem. In 1892 a boy, aged 3 months, was admitted with bronchitis. He was the eighth child, and was born at full term, the delivery being easy. When three weeks old he had convulsions, which continued for seven days. On admission, the infant was wizened, the cranial sutures were pronounced, but no mention is made of any paralysis; the bronchitis progressed to broncho-pneumonia, and he died three weeks after admission. At necropsy, the convulsions of the left parietal lobe were atrophied and stained yellow. At the posterior part of the right lateral ventricle was a cavity with disintegrated walls, extending upwards into the substance of the hemisphere. The wall of this cavity contained haematoidin crystals and cells containing blood pigment.

The following case would appear to be one of cerebral haemorrhage with recovery: A male child, aged 3 weeks, was admitted to the Hospital for Sick Children. The child was the first-born of healthy parents, the labour lasted thirty-six hours, and instruments were used. From the ninth to the eleventh day, the child had five convulsions, leaving him with left-sided facial paralysis and inability to suck or cry. On admission, the child lay quite apathetic, with the head rigidly turned towards the left shoulder. The limbs were rigid, and the legs adducted and crossed. The left side of the face was weak, and the child remained silent even when repeatedly stimulated. The circumference of the head was $15\frac{1}{2}$ inches, the posterior fontanelle was open, the anterior fontanelle tense, bulging, and without pulsation. The movements of the right eye were well performed, but the left eye was stationary, so that there was present a squint of varying degree. The left pupil was larger than the right; the optic disks were normal. The cerebro-spinal fluid was straw-coloured, with a gelatinous clot; albumin, 0.3 per cent.; chlorides, 7.2 grm. per litre; cells, 25 per c.mm., of which 75 per cent. were mononuclears. The fluid was sterile, and its Wassermann reaction negative. The child remained under observation for ten weeks, during which time he improved slightly; the limbs, especially the legs, remained very rigid, and the inequality of the pupils persisted. The facial paralysis disappeared after a few weeks. Seen five months later, the child was growing well, but the limbs remained stiff, the fingers were always clenched, and the thumbs turned into the palms. The eyes, in company with the eyelids, made constant twitching movements of a convulsive nature. The child took practically no notice, and it was doubtful whether it could see.

The history of the case resembles the early history of many cases of spastic diplegia found in later childhood. McNutt (7), in 1885, collected thirty-four cases of spastic diplegia with post-mortem findings. All the cases showed some defect of the cerebral cortex on one or both sides, situated at, or near, the motor area.

In the majority of the cases the defect consisted of atrophy, and in many there was definite evidence of previous haemorrhage in the form of actual blood-clot or yellow staining of the cortex.

Although most of the haemorrhages in early infancy originate from birth, this is not necessarily so. East's case, previously mentioned, was of quite uncertain origin. Congenital syphilis is occasionally associated with a haemorrhagic state, although generally the bleeding is not intracranial. One of our cases was a congenital syphilitic. The mother of the child had had two previous miscarriages, and the child when three weeks old passed a quantity of blood per vaginam. On admission next day the child was jaundiced, the nose was bleeding, and there was blood in the stools; blood was oozing from the vagina. The child's Wassermann reaction was positive. Death ensued two days later, and at autopsy a subarachnoid haemorrhage was found over the left motor cortex.

Two of our cases were associated with icterus neonatorum. Both infants had been jaundiced since birth, and in neither was there reason to suspect syphilis. In both the haemorrhage appeared too recent to have dated from birth. One died when three weeks old; during life the child had some purpuric spots on its extremities, and the spleen reached nearly an inch below the costal margin. The Wassermann reaction was negative. At post-mortem examination extensive recent blood-clot was found beneath the dura mater over the vertex of the brain, and in the three cranial fossae. The other child died at the age of six weeks, having had a convulsion on the day before death. In this case the spleen was not palpable. At post-mortem examination a recent subdural haemorrhage was found over the whole of the left hemisphere. There was also haemorrhage into both suprarenal bodies.

A case in which the jaundice was due to congenital obliteration of the bile-ducts was recorded by Gladstone (8). The child died when eight weeks old, and at autopsy within the left hemisphere near the internal capsule was a blood-clot as large as a pigeon's egg, with an equal amount of semi-clotted blood.

None of our cases of subdural haemorrhage occurring in infants showed encapsulation of the clot with a newly formed vascular membrane, corresponding to the so-called haemorrhagic pachymeningitis of infants.

Haemorrhages arising after the Natal Period.

Of the haemorrhages found in older children—the postnatal group—some are traumatic. Three of our cases were of this nature; in two, the haemorrhage had taken place within the brain substance, one in the centrum ovale, the other in the medulla; in the third case the middle meningeal artery had ruptured.

The first case dated from a fall against a cupboard a few weeks previously. On the day of admission, the child vomited and then became unconscious; later in the day, the right arm and leg were noticed to be making choreiform movements, whilst the left arm and leg were paralysed. Death took place three hours after admission, and at autopsy there was found a large clot in the right internal

capsule. Part of the clot was adherent to the surrounding cavity and apparently of some standing. The haemorrhage had burst through the cortex at the island of Reil, and the surface of the brain was covered with recent clot.

In the second case, two days before death the child hit his head against a table. He complained of headache, and was sick. During the brief time he was under observation, he was noticed to have no motor or sensory paralysis, but had slight retraction of the head. At post-mortem, there was found a haemorrhage in the medulla; the blood had burst into the fourth ventricle, and thence had spread over the posterior surface of the medulla. Apart from the haemorrhage, the body was normal. (See Pl. 4, Fig. 1.)

The third case was that of a boy who fell off a kitchen chair; the child became unconscious after a quarter of an hour, and three hours later the right arm and leg showed convulsive movements, which were followed by paralysis. Within five hours of the injury the skull was trephined over the left middle meningeal artery, and on opening the dura mater a large amount of fluid blood escaped. The child died a few hours later, and at autopsy no fracture of the skull could be found, nor was the brain lacerated.

Some of the cases of traumatic haemorrhage have a considerable latent period between the time of the injury and the onset of symptoms. The first of our three cases showed a period of a few weeks between the time of the fall against a cupboard and the vomiting and loss of consciousness, which preceded death by only a few hours. A similar case was that of a boy, aged 6 years, who was admitted into King's College Hospital under the care of Dr. Still. He had been knocked down by a horse four days previously, but had remained well until the day of admission, when he had a convulsion followed by loss of consciousness. On admission he had a complete left-sided hemiplegia. He died the following day, and at autopsy a large haemorrhage was found into the right internal capsule. Both lateral ventricles also contained blood.

Miller (9) recorded the case of a girl, aged 12 years, who was struck on the left side of the head by a stone held in the hand of another girl. For a few hours she was a little dazed, but soon recovered. Seven weeks and one day later she died rather suddenly, and an extensive subdural haemorrhage was found over the vertex of both hemispheres. The under-surface of the temporo-sphenoidal lobe showed a small area of softening and necrosis, but there was no evidence of injury to the skull.

There are cases on record in which children have died suddenly for no apparent reason, and at post-mortem examination extensive cerebral haemorrhage has been found. Hawthorne (10) described two such cases in boys aged 14 and 17 respectively, in neither of whom could any history of trauma be obtained. He also collected twelve similar cases in children and young adults; in seven death speedily followed upon the initial symptoms, in five the symptoms lasted over several days. In three of the cases there was found at autopsy evidence of renal disease, but in the others there was neither renal nor vascular disease. It is possible that in these cases there was some earlier violence, slight in degree,

but sufficient to start a process of softening and necrosis which culminated in a fatal haemorrhage.

Amongst the possible sources of trauma in producing a meningeal haemorrhage are ventricular, cisternal, and lumbar puncture, although such accidents must be very rare. In two of our cases meningeal haemorrhages were found after death, and the question arose whether the previous punctures had played a part in this production. In one case a child of 5 months died of tuberculous meningitis; at intervals up to two days before death lumbar puncture had been performed, and at autopsy blood was found surrounding the pons and medulla. The blood was in continuity with a haemorrhage extending the whole length of the posterior surface of the spinal cord in the subarachnoid space.

The other instance was a child, aged 5 months, who died of post-basic meningitis. Antimeningococcal serum had been given intrathecally by the lumbar route, and two days before death a ventricular puncture had been carried out. At post-mortem examination there was a recent extravasation of blood on the surface of the right hemisphere, at the site of the ventricular puncture. There was also some altered blood in the cisterna magna, and the anterior surface of the spinal cord along its whole length showed a continuous layer of blood-clot.

Haemorrhage associated with Chronic Nephritis.

One of the commonest causes of cerebral haemorrhage in adults, and one of the rarest in children, is chronic interstitial nephritis; very few cases are on record of children with this disease dying of cerebral apoplexy. A case was recorded by Guthrie (11) of a girl, aged 7 years, who showed symptoms of chronic interstitial nephritis, and during the last five weeks of her life had three convulsions. At autopsy the kidneys were contracted and granular, the cortex being hardly recognizable. The walls of the arterioles of the meninges and brain were definitely thickened. On opening the brain two haemorrhages were found in the right hemisphere; one as large as an egg was situated in the centrum ovale, the other in the occipital lobe was the size of a golf-ball.

In one of our cases chronic interstitial nephritis was also present. The patient, a girl, aged 12 years, had had measles, whooping-cough, chicken-pox, and scarlet fever. For two months before admission she had frequent headaches and attacks of vomiting. On the day after admission she complained of severe headache, and became restless; five hours later she was unconscious, the pupils were unequal and the heart action violent. Death followed within an hour. At autopsy the kidneys were very contracted, the renal capsules were universally adherent, and no division of the kidney substance into cortical and medullary portions could be made out. In the brain, within the substance of the left occipital lobe was a cavity as large as a goose's egg, filled with clot. The blood had extended to the surface of the brain, and internally had ruptured into the lateral ventricle. The arteries at the base of the brain were normal.

Haemorrhages associated with Diseases of the Blood.

The next group of cases to be considered are those in which intracranial haemorrhages were found in association with the various blood disorders of childhood. In most of the cases the haemorrhage was subdural and extensive, while in a few cases smaller but definite haemorrhages were found within the cerebellum.

One of the cases was a boy, aged 3 years, who died of acute lymphoid leukaemia. The disease ran a course of two months; the lymphatic glands in the neck, axillae, elbows, and groins were enlarged, the spleen extended two fingers breadth below the costal margin, and the trunk and limbs showed many petechial haemorrhages. A blood-count showed: red blood-corpuscles 1,340,000 per c.mm.; haemoglobin 32 per cent.; leucocytes 14,000 per c.mm., of which 96 per cent. were lymphocytes. At post-mortem, the dura mater over the vertex of the brain was the site of several large areas of haemorrhage, apparently due to bleeding from the capillaries.

No evidence of intracranial haemorrhage was forthcoming in the post-mortem records of cases of myelogenous leukaemia or acute leukanaemia.

A similar haemorrhage to that of the last case was found in a child who died of splenic anaemia of infancy (Von Jaksch's anaemia). The patient, a girl aged 13 months, was admitted to hospital for anaemia, which had been gradually getting worse for six months. When in hospital the child was obviously anaemic, with petechiae in the skin, and the spleen extended below the umbilicus, bulging the left flank; the liver was enlarged to a less degree. Blood examination showed: red corpuscles 2,280,000 per c.mm.; haemoglobin 45 per cent.; leucocytes 44,000 per c.mm., of which 34 per cent. were polymorphs, 53 per cent. lymphocytes, and 6 per cent. myelocytes; several normoblasts were also present. The child died five weeks after admission, and at autopsy, in addition to a large tough spleen, profuse haemorrhages were found in the subdural space over the vertex of the brain.

In three fatal cases of purpura haemorrhagica, one a boy aged 5, and two aged 3 years, several small patches of haemorrhage were found beneath the dura mater. In one of these cases there was also a blood-clot as big as a walnut extending from the surface of the right lobe of the cerebellum down into the white matter; the third ventricle contained a small blood-clot.

Two other children, both aged 4 years, were admitted some 40 years ago complaining of severe anaemia. In one the cervical glands were enlarged, and the skin of the trunk and limbs was dotted with petechial haemorrhages and larger bruises; the spleen was not palpable. A blood-count showed one and a half million red cells per c.mm. Death ensued in three weeks. In the other, there were enlarged glands in the neck, axillae, and groins; the spleen could not be felt; several small retinal haemorrhages were seen, but no mention is made of any petechiae in the skin. There were two and a half million red cells per c.mm., and 20,000 white cells per c.mm. This child lived for ten days. In both of

these cases several small haemorrhages were found, confined to the surface, and within the substance of the cerebellum.

Another condition which may conveniently be considered here is Hodgkin's disease. The later stages of this disease are marked by anaemia, which may be profound, and a tendency to bleeding. One of our cases, admitted in 1887, suffered from lymphadenoma. The patient was a girl, aged 10 years, who for twelve months had had gradually enlarging glands in the neck. In hospital, in addition to the enlargement of the cervical glands, the spleen was noted to be two fingers breadth, and the liver three fingers breadth below the costal margin; petechiae appeared in the skin, and three months after admission the child died. At post-mortem examination the lymph glands in the neck and abdomen were enlarged and faintly pink on section; the liver and spleen contained bosses of lymphadenomatous tissue. Within the skull there was a symmetrical subdural haemorrhage overlying both parietal lobes, and extending downwards into both temporal fossae.

It will be noticed that in these cases forming the group of blood disorders, the haemorrhages, although in some cases extensive, were of themselves hardly sufficient to prevent recovery, and scarcely severe enough to have been the principal factor in causing death. This is in accordance with what would be expected from a comparison of these with the small cutaneous haemorrhages which occur in these diseases. The larger haemorrhages would probably be brought about by the confluence of several smaller ones.

Two diseases in which the principal symptoms are due to haemorrhage are scurvy and haemophilia. In both of these haemorrhages into the brain are said to occur, but such an occurrence is very much the exception. With regard to scurvy, at the present day very few cases are fatal, but at autopsy on nineteen cases at the Hospital for Sick Children, intracranial bleeding had not occurred in any. In the literature of the subject recorded cases are remarkably rare. In 1894 Ord (12) reported the case of a boy, aged 11 months, who, whilst under treatment for scurvy, developed an acute infection of the gastro-intestinal tract, which in its turn became complicated by broncho-pneumonia. At the post-mortem, a bright red subdural haematoma was found over the vertex of the brain. In another case recorded by Sammis (13), a child, 12 months old, admitted to hospital with scurvy died ten days later with a convulsion. At autopsy, in addition to haemorrhages elsewhere, there was between the dura mater and the arachnoid over the left post-central gyrus a blood-clot measuring $2\frac{1}{2}$ inches in length and half an inch in breadth.

Cases of cerebral haemorrhage in haemophilia are even more rare. None of our cases suffered from haemophilia. Byrom Bramwell (14) recorded the case of a youth, aged 18, thought to be haemophilic, who slipped while skating and alighted in a sitting position. For several days he complained of headache, and five days after the accident vomited. These symptoms continued for a fortnight, and then he became completely blind and unconscious, with weakness of the left side of the face and left arm; the fundi showed papilloedema. The fall was

thought to have caused effusion of blood at the base of the brain with some resulting meningitis. The patient made a gradual recovery.

Another instance of cerebral haemorrhage in a haemophilic child was reported by Harper (15).

Haemorrhages associated with the Acute Fevers.

Certain of the acute exanthemata are said to be sometimes complicated by meningeal or cerebral haemorrhage, and in particular scarlatina, measles, varicella, typhoid, and whooping-cough are mentioned in text-books as very occasionally showing evidence of intracranial haemorrhage; reference to actual cases is, however, very scanty, and the opportunity of confirming the diagnosis of haemorrhage at post-mortem seems very seldom to have arisen. One of this series occurred during whooping-cough, another during varicella.

The case of whooping-cough has been previously recorded by Langmead (16). A girl, aged 2 years, admitted for whooping-cough with broncho-pneumonia, two weeks later developed twitching of the left eyelid and left upper limb, and the next day of the right side also, and died the following day. *Post mortem* the veins over the vertex of the brain and the cerebral sinuses were engorged and filled with red blood-clot. In the subarachnoid space was a layer of haemorrhage extending over the whole of the upper surface of the right hemisphere, and over the anterior two-thirds of the left (see Pl. 4, Fig. 2). As will be shown later, thrombosis of the cortical veins, with surrounding haemorrhage, may be found after death from broncho-pneumonia quite apart from the occurrence of whooping-cough, although in such cases the haemorrhage is not usually so extensive as in this particular instance. It is possible therefore that in this case the thrombosis resulted from the broncho-pneumonia—which had been present for at least fourteen days—and the whooping-cough may have assisted in producing rupture of the turgid veins.

In the case of varicella, the child, a girl aged 5 years, was first admitted with purpura haemorrhagica, which had been present and getting worse for two months. On admission there were petechial spots and bruises over the trunk and limbs, the gums bled easily, and there was blood in the urine. Three weeks later the child went to a convalescent home, whence she returned after ten days, covered with a typical varicella rash. After readmission each vesicle 'became purple, with a zone of purple extravasation around it'. Presumably haemorrhage occurred into the vesicles. Four days later the child had convulsions and died. *Post mortem* the purple vesicles of the varicella rash were noted. Most of the viscera showed minute punctiform haemorrhages, but in the subdural space over the right hemisphere was an extravasation of blood, irregular in shape and 'larger than two crown-pieces'.

Steiner (17) states that in the haemorrhagic variety of variola—the so-called black small-pox—at post-mortem, in addition to extravasations in the skin

and mucous surfaces, meningeal and cerebral extravasations may be found, and he considers that the haemorrhages in these cases may possibly result from an acute fatty degeneration of the vessels.

Haemorrhages in Association with Heart Disease.

As in adults, so in children, heart disease may be associated with cerebral haemorrhage. The haemorrhage results from the occlusion of an artery or its branches by an embolus, and by far the commonest type of heart disease to produce emboli is infective or malignant endocarditis. In eight out of our fifty cases the haemorrhage resulted from embolism during the course of malignant endocarditis, and of these seven were between the ages of 8 and 11 years, the remaining child being ten months. In this case the acute endocarditis was grafted upon a congenital malformation of the heart.

In two cases the malignant process was not preceded by any definite rheumatic infection. In one of these there had been joint pains for six weeks; on the day of admission, the child had a convulsion which left her aphasic, with a right hemiplegia. Death occurred six weeks later, and at autopsy, in addition to large fleshy vegetations on the mitral and aortic valves, and on the mural endocardium of the left auricle, there was a haemorrhage beneath the base of the brain in the interpeduncular fossa, and the left motor area was depressed and stained yellow. The brain was preserved unopened.

In the second instance, the history of cough and sickness dated from three days before admission; on admission, the heart was hypertrophied and the spleen enlarged. Death, which followed in five months, was preceded seven days previously by a stroke, leaving the child with left hemiplegia. At post-mortem there was a recent large haemorrhage beneath the right motor cortex.

In five cases there was a preceding history of rheumatic infection; thus one child had had frequent attacks of acutely swollen joints; another had acute rheumatism five months before admission, and during the interim had been breathless; a third child had had two attacks of chorea, whilst in two cases there was a history extending over two years of rheumatic heart disease. Nevertheless at autopsy there were found in all the large soft vegetations typical of acute infective endocarditis.

In three of these five cases, at some period within the twenty-four hours before death, the patient suddenly complained of headache, vomited, and lost consciousness; convulsive movements and paralysis immediately preceded death. In every case there was found at post-mortem a large haemorrhage within the substance of one or both hemispheres, the lateral ventricles contained blood, and the haemorrhage had reached the exterior of the brain, blood being seen in the subarachnoid space, either covering the hemispheres or in the posterior fossa (see Pl. 4 and 5, Figs. 3 and 4). In none could the actual site of an embolus be determined.

In the instance of the child aged 10 months, an embolus was found. This

child was admitted with faucial diphtheria; the heart was enlarged and there was a faint systolic murmur heard equally all over the præcordium; the extremities were cyanosed, but there was no clubbing of the fingers. The diphtheritic process speedily cleared up, but the child gradually succumbed to progressive cardiac failure. Within the twenty-four hours before death, three convulsions occurred. *Post mortem* there was stenosis of the pulmonary artery with patency of the interventricular septum; recent vegetations were found on the mitral and tricuspid valves. On the brain, over the left parietal lobe, was a blood-clot as large as a walnut, and the greater part of the left hemisphere was disintegrated by a big haemorrhage. The left middle cerebral artery was found blocked by a recent embolus.

Looking back over these eight cases, three features stand out prominently. The haemorrhage was chiefly within the substance of the brain—in the one case in which the brain was unopened, there was almost certainly a haemorrhage within; in all cases the haemorrhage was large; the haemorrhage was the immediate factor in causing death. Owing to these three characteristics, the haemorrhages presumably resulting from embolism are more likely to lead to cerebral symptoms and to determine a fatal result than those in association with the various blood disorders.

Haemorrhages secondary to Thrombosis.

Of the various factors that may play a part in the production of intracranial haemorrhages in children, the most common immediate precursor was found to be thrombosis of the vessels in the meninges or brain, or of the sinuses, and the eighteen cases illustrating this condition have been grouped together, although the nature of the diseases that gave rise to the thrombosis differed widely. In the post-mortem records of four of these children actual mention is not made of thrombosis having been found, although from the evidence which will be brought forward it may be fairly presumed that the haemorrhage arose as a result of thrombosis. The site of the haemorrhage is of interest: in eleven cases the blood was extravasated in the subarachnoid space, usually over the vertex of one or both hemispheres, and in all these either the cortical veins or sinuses contained clot; in five, the bleeding was confined to the substance of the brain, and in at least one of these the thrombus occupied the lumen of an artery; in two, blood was found both within the brain substance and in the subarachnoid space.

The cases of thrombosis fall into two groups, marantic and infective. Marantic thrombi are found in extremely wasted or debilitated children, in whom a feeble heart-action gives rise to a sluggish blood-stream, thereby favouring the production of thrombosis, and aided in some cases by the presence in the blood of toxic products of metabolism, or bacterial toxins arising from inflammatory processes in some other part of the body. The majority of our cases have followed this type of thrombus; the remainder were due to an

infective thrombosis complicating some inflammatory lesion of the brain and its coverings.

Amongst the rarer causes of marantic thrombosis is congenital hypertrophy of the pylorus. A boy who died at the age of 11 weeks, after Loreta's operation for pyloric stenosis, showed at autopsy thrombosis of the superior longitudinal sinus and its tributary veins. There was an extravasation of blood in the subarachnoid space over the right hemisphere and in the posterior fossa; small areas of haemorrhage were found in the left corpus striatum.

In two cases the thrombosis leading to haemorrhage was associated with cleft palate. A boy, aged 4 weeks, who died after an operation upon cleft palate, was found to have a subarachnoid extravasation about the size of a shilling at the posterior part of the superior frontal gyrus on the right side; the superficial veins in the immediate neighbourhood were thrombosed. The other child was 16 days old, and for two days before death had retraction of the head. Extensive thrombosis was found in the cortical veins, the superior and inferior longitudinal sinuses and straight sinus, and in the veins of Galen. The substance of the hemispheres was destroyed by haemorrhage, and the lateral ventricles were filled with blood-clot.

In two cases the general debility and wasting that accompanies tuberculosis were responsible for the cerebral thrombosis.

A boy, aged 2 years, was admitted with tuberculous peritonitis and ascites; after being in hospital two months, he became suddenly worse and was sick, the eyes were deviated to the left, and the pupils contracted to pin-point size. Death followed in a few hours; advanced plastic tuberculous peritonitis was found. There was no evidence of tuberculous meningitis, but the basilar vein was thrombosed and haemorrhage had taken place into the lower part of the pons.

In the second case, a boy aged $2\frac{1}{2}$ years, in hospital for tuberculous pleurisy, after exerting himself in the effort to change his pillow, immediately became hemiplegic on the right side. After five days he died, and, in addition to tuberculosis of the lungs and mediastinal glands, there was found a small haemorrhage into the left internal capsule. No clot could be discovered in the middle cerebral arteries, but there was 'slight recent thrombus in the sinuses'. The haemorrhage may possibly in this case have resulted from an embolus originating from the disease in the thorax, and the rapidity of onset of the hemiplegia following exertion lends some support to this view.

Thrombosis was secondary to prolonged sepsis in a boy aged 4 years, who was admitted with an advanced septic arthritis of the right knee, the result of a fall fourteen months previously. Two months before admission, an abscess over the knee had burst; in hospital the joint was opened and much pus evacuated; the pus had tracked widely, and counter openings were necessary in the thigh, popliteal space, and over the calf muscles. Three weeks later, the right side of the face became weak, papilloedema was discovered, and within four days the child died. At autopsy the knee-joint was thoroughly deranged,

the synovial membrane and cartilage had disappeared, and the bone ends were much eroded. In the cranium, the superior longitudinal sinus and its tributary veins, the lateral sinus and the straight sinus, were plugged with firmly adherent, partly decolorized blood-clot; within the brain, the left centrum ovale was torn up by a large clot occupying quite two-thirds of the white matter.

Pneumococcal infections, as part of their general tendency to give rise to thrombosis, produce in some cases cerebral thrombosis with resulting haemorrhage. This was found in five cases—two of broncho-pneumonia, one of lobar pneumonia, and two of empyema. It is possible that the toxins of the pneumococcus circulating in the blood-stream may in some way increase the liability to clot-formation, and the congestion and stasis of the blood-flow consequent upon the straining of the right side of the heart would probably increase the likelihood of this accident. Moreover, it is probable that in some cases pneumococci in the blood-stream become lodged at some point in the vessel, and set up thrombosis.

Of the two instances with broncho-pneumonia, one child, aged 4 months, died after a week's illness. On the day before death, the head was noticed to be retracted, and there was an internal strabismus of the right eye. At post-mortem examination, the left motor area and neighbouring cortex were covered with a large subarachnoid blood-clot, out of which emerged thrombosed cortical veins (see Pl. 5, Fig. 5). The other child, aged 7 months, died after three days' illness, and was found to have—in addition to patchy consolidation of both lungs—a subarachnoid extravasation as large as a five-shilling piece over the right Rolandic area. Mention is not made of thrombosed vessels being seen, but it is difficult to understand how otherwise the haemorrhage could have arisen.

The case of lobar pneumonia occurred in a boy aged 11 months; fourteen days before admission, he had a convulsion, and six days later several more fits. In hospital, besides physical signs of consolidation of the right lung, he showed slight head retraction, internal strabismus of the left eye, rigid extension of the right hand and fingers, and bilateral extensor plantar reflexes. At autopsy the right lung was solid, the superior longitudinal sinus and lateral sinuses were thrombosed, and there was an extensive subarachnoid clot over the left frontal and parietal lobes.

Of the cases of empyema, one was a boy aged 12 months, who lived only two days after admission to hospital; several convulsions occurred on the day before death, and at later examination the superior longitudinal sinus and its tributary veins were thrombosed, and there was a large area of haemorrhage in the subarachnoid space over the left parietal occipital and temporo-sphenoidal lobes.

The other infant, a boy aged 9 weeks, was admitted with pneumonia; ten days later the patient had a convulsion and died on the following morning. He was found to have consolidation of both lower lobes, and about half an ounce of thin pus in the right pleura. The superior longitudinal sinus and the veins draining into it were filled with dark red, slightly adherent clot, and over the

right Rolandic area in the pia arachnoid, over an area about two inches square, was a sheet of haemorrhage. This case is of further interest because a thin flake of pus, found between the cerebellum and medulla, proved on examination to contain pneumococci, so that there was a condition of very early suppurative meningitis. This can scarcely have been sufficient to have determined the extensive sinus thrombosis.

In a child, aged one year, who died of broncho-pneumonia in King's College Hospital, while under the care of Dr. Still, the left pleura was found to be covered with lymph, and the whole of the left lobe of the cerebellum was covered by a recent haemorrhage beneath the pia arachnoid.

It will be noticed that of the ten cases of thrombosis occurring in wasting conditions, or in inflammatory processes in tissues other than the cranial contents, the superior longitudinal sinus has been implicated in six instances, which seems to indicate that this channel is particularly liable to be the site of formation of a marantic thrombus.

There were five further cases in which haemorrhage complicated an inflammatory disease of the brain or its coverings. One was in a child, aged 2 months, who had suffered from frequent convulsions since eight days old. The infant died soon after admission to hospital, and was found to have thick lymph over the base of the brain; the superior longitudinal and lateral sinuses were thrombosed and a large meningeal haemorrhage had taken place over the cortex just posterior to the left motor area. In the centre of the haemorrhage was a thrombosed vein. The causal organism of the meningitis was not determined.

The four other instances occurred in children who died of tuberculous meningitis. The clinical picture gave no indication that haemorrhage had occurred, nevertheless in two cases extravasation of blood had taken place into the subarachnoid space over the left frontal lobe, covering an area as large as a crown-piece, and in a third child there was a clot of blood the size of a bean in the vermis of the cerebellum. In these three, mention is not made of any thrombosed vessels, although it is probable that the thrombosis of a capillary or small vein preceded the haemorrhage.

The fourth case supplies an example of arterial thrombosis. At autopsy the brain showed the characteristic appearances of tuberculous meningitis and in addition an extensive area of softening in the right hemisphere, reaching from just under the cortex of the frontal lobe at its anterior extremity to the hinder part of the Rolandic area. The brain substance was breaking down and diffuent, and into it a considerable haemorrhage had taken place. A branch of the right middle cerebral artery supplying this area was blocked by a thrombus.

Two cases of our series are difficult to classify. One was a boy of 11 years, who died of diabetic coma, and on the surface of the brain beneath the pia arachnoid covering the frontal lobes were a few extravasations of blood. The other was a girl aged 8 years, who was admitted with well-advanced pseudo-

hypertrophic paralysis. For four days she had incessant vomiting, and two days later the optic disks were found congested and the vessels tortuous; within twenty-four hours she collapsed and died, and at autopsy on the surface of the pons and medulla a thin layer of blood-clot was found; the rest of the brain was normal.

Diagnosis.

In the majority of the cases collected here, the intracranial haemorrhage was not diagnosed before death, and indeed hardly could have been when the haemorrhage was a terminal event. In some of those where it occurred days or weeks before death, e.g. in cases of malignant endocarditis and trauma, intracranial haemorrhage, if not actually diagnosed, might have been suspected.

One symptom that seems fairly common is the occurrence of convulsions, and it may be presumed that these indicate approximately the time at which the haemorrhage occurred. In this series a positive statement of convulsions is made in 59 per cent. In those diseases in which convulsions were found to have been the first indication of cerebral haemorrhage, it was noticeable that the convulsion was not an initial or early occurrence in the disease, but appeared when the illness was already advanced. The convulsions were seldom of localizing value, but the paralysis which followed in some cases corresponded more closely to the area of haemorrhage.

A combination of irritative and paralytic symptoms may be the indication of haemorrhage. A boy, aged 5 months, suffering from acute infective gastro-enteritis, was noticed one morning to be suddenly worse. The left side of the face was paralysed, the left cheek puffing out with each breath; the eyes were actively deviated towards the right side, and the pupils were of pin-point size. The arms were stiff and making continual fighting movements, the legs were rigid and the knee-jerks unduly brisk. A diagnosis was made of meningeal haemorrhage pressing upon the pons, and a cisternal puncture was performed; the cerebro-spinal fluid was under increased pressure, and pink in colour from the uniform admixture of blood in it. Following the puncture and relief of pressure, the movements of the arms and eyes ceased, only to return a few hours later when the child died. Unfortunately permission for a post-mortem examination was refused, but it is very probable that the bleeding was the result of a marantic thrombosis of a cerebral sinus or meningeal vessel.

The signs of cerebral irritation or paralysis are generally rapid in onset, but not necessarily so. A child, aged 16 months, who had been treated for a fortnight for suppurative meningitis due to the pneumobacillus of Friedländer, was noticed one day to be having convulsive movements of the left side of his face and left arm. The twitchings gave place to weakness of the parts affected, which gradually increased in severity during the ensuing five days, when death occurred. It had been feared that a collection of pus was forming, but at autopsy the signs were found to result from thrombosis of the superior

longitudinal sinus and its tributary veins, with a subarachnoid haemorrhage spreading over the right motor cortex.

In some of those cases in which life has continued for a few days after the initial symptoms of haemorrhage, examination of the fundus oculi has shown swelling of the disks; the signs of meningeal irritation, such as retraction of the head and Kernig's sign, have also been noted in several of the cases.

The post-mortem evidence shows that, although in some cases, notably those with malignant endocarditis, the situation and extent of the haemorrhage was sufficient *per se* to have resulted in death, in others the patient died because of the severity of the primary disease, and but for that, could have recovered from the lesion produced by haemorrhage. Areas in the brain of yellow staining by altered blood-pigment indicate a previous haemorrhage.

The possibility of recovery from the haemorrhage has already been pointed out in the group of blood disorders, and McNutt has shown this to occur in haemorrhage produced at birth; recovery may also take place in some instances of haemorrhage secondary to thrombosis.

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FIG. 1. Brain of boy aged 3 years, showing haemorrhage into the medulla, the fourth ventricle, and the subarachnoid space ventral to the medulla. The result of trauma.

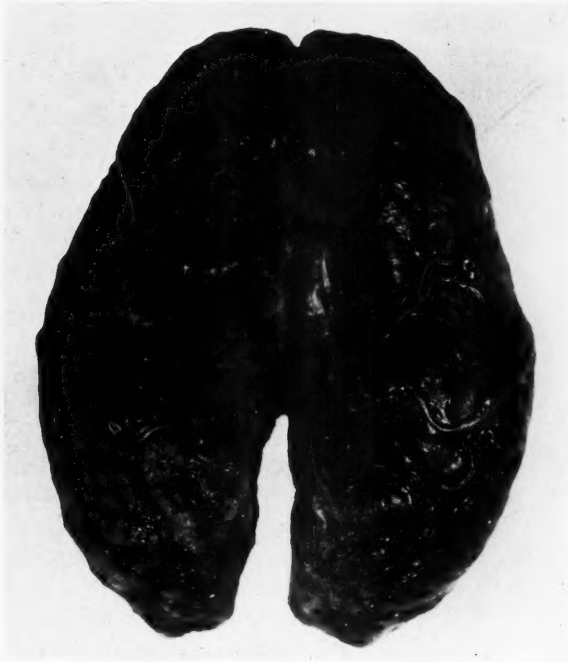


FIG. 2. Brain of girl aged 2 years, showing thrombosis of meningeal veins, and diffuse subarachnoid haemorrhage over both hemispheres. The result of whooping cough and bronchopneumonia.

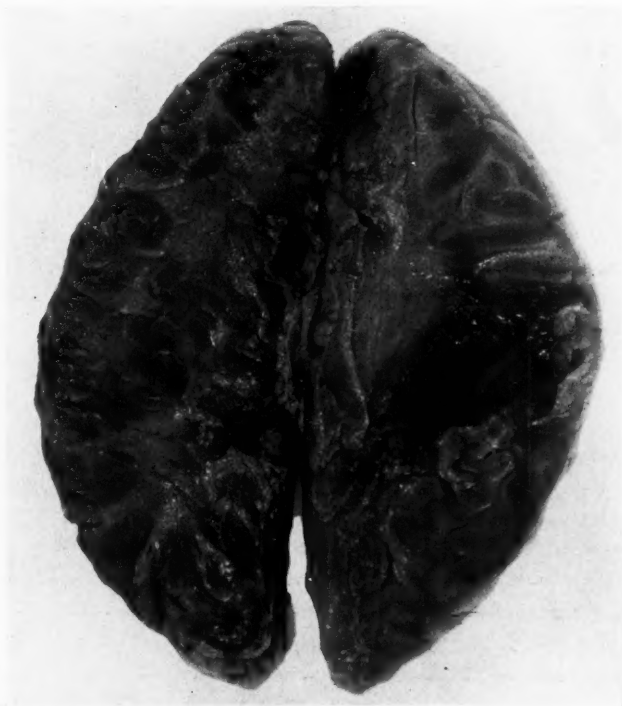


FIG. 3. Brain of boy aged 10 years, showing extensive blood clot in the centrum ovale of right hemisphere. The result of malignant endocarditis.



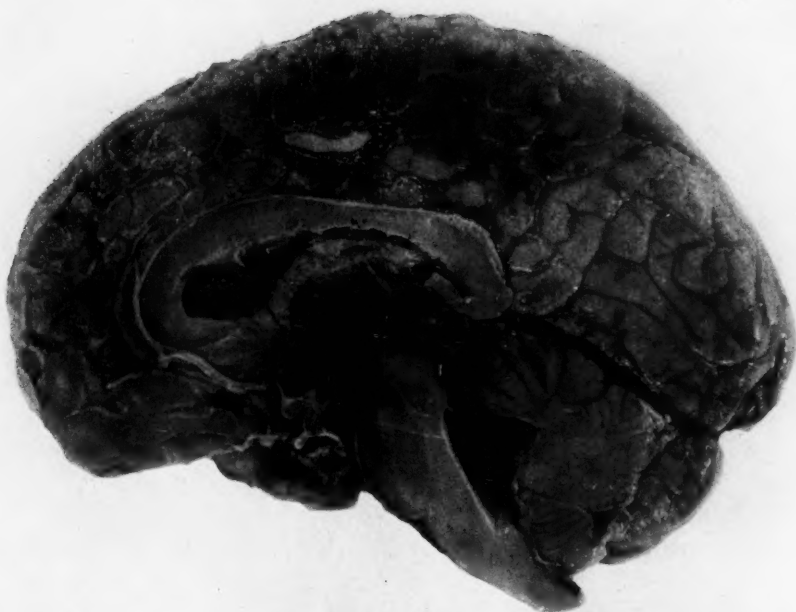


FIG. 4. Brain of girl aged 9 years, showing haemorrhage in lateral ventricle, third ventricle, iter, and fourth ventricle. There is a subarachnoid extravasation over inner surface of parietal lobe. The result of malignant endocarditis.



FIG. 5. Brain of girl aged 4 months, showing haemorrhage over the left frontal lobe; the meningeal veins in the immediate neighbourhood were thrombosed. The result of broncho-pneumonia.

THE SEDIMENTATION-RATE OF ERYTHROCYTES IN CERTAIN TROPICAL DISEASES¹

By H. B. NEWHAM

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CONSIDERABLE attention has been focused of late years on the phenomenon of the sedimentation of the red-blood corpuscles and the rapidity or otherwise with which the cells' sediment has been observed in a number of different cases of disease. Although the fact that the rate of sedimentation varied in different bloods and in different diseases was known to many of the older physicians, including John Hunter, still credit for bringing the matter forward must be given to Fåhræus, (1) who, in 1918, published a monograph on the subject, and much work on the reaction has since been done by Linzenmeier (2), Löhr (3), Hoffgaard (4), Westergren (5), &c.

Their observations have chiefly been made on cases of pregnancy, acute inflammations, malignant disease, and tuberculosis, and it is particularly on the last named that most work has been done. It is suggested that repeated observations of the sedimentation-rate in cases of tuberculosis are of value in gauging the progress of the disease and in forming a prognosis. Thus Popper and Kreindler (6) examined 250 patients and found that all progressing pulmonary affections showed an increased sedimentation. Morris and Rubin (7) have applied the test to 400 cases and find that the sedimentation-rate shows close agreement with the clinical manifestations. On the other hand Wingfield and Goodman (8), working on 156 cases of tuberculosis, came to the conclusion that the sedimentation-rate in that disease gives little or no information that cannot be elicited by careful clinical observation. Little work has, however, been done on the subject in regard to cases of tropical disease.

A few observations have been recorded. Gilbert and others (9) have studied the phenomenon in six cases of leprosy, and the results show that an increased rate is noted in that disease. Landeiro (17) has also made observations of the sedimentation-rate in fifty cases of leprosy, both of the anaesthetic and tubercular types, and the results obtained will be referred to later. Stühlman (10) and Marie Thomas (11) have both noted definite increases in the sedimentation-rate in cases of malaria, whilst the latter also states that hookworm disease affects the rate in the same way.

¹ Received December 8, 1926.

Technique.

Various methods of estimating the sedimentation-rate have been adopted by different observers. Thus Fåhræus employs tubes of 17 cm. in length with an internal diameter of 9 mm., Linzenmeier uses tubes of 6.5 cm. in length and 5 mm. internal diameter, whilst Westergren employs tubes of 30 cm. in length and of an internal diameter of 2.5 mm. Moreover, different workers have used different methods of recording their results, some relying on noting the height of the column of sedimenting cells at varying periods of time, whilst others record the depth of the column of superjacent plasma above the corpuscles. In working with tubes of small internal bore it was felt that possibly capillary attraction and other factors might enter into the reaction, and moreover my experience has been that with such small-bore tubes there often arose difficulties in making exact readings. In the results to be recorded and discussed later I have adopted the method advised by Cooper (12). He employs 15 c.c. graduated centrifuge tubes. The blood is oxalated with the minimum amount of *dry* potassium oxalate necessary to prevent coagulation, thus avoiding any dilution of the blood such as occurs when using either a solution of potassium oxalate or of sodium citrate. The readings are all expressed in terms of the height of the column of sedimenting cells. Five c.c. of the oxalated blood are placed in the tube and readings taken at 10, 20, 30, 40, 50, 60, and 120 minutes from the time of starting.

Theories of the Phenomenon.

In investigating the phenomenon of the varying sedimentation-rate in different disease conditions the object of my investigation was primarily to determine, if possible, the factor or factors responsible for variations in rate, and, secondarily, by determining the varying rates in different diseases, to ascertain if such would give any assistance in differential diagnosis.

Various views have been put forward to account for the great variability in sedimentation-rate. Thus, some authorities suggest that rapid sedimentation is due to an increased cholesterol content of the blood. Others think that the cause is an increase in the fibrinogen content, whilst others again ascribe the phenomenon to an increase in the serum globulin, with a corresponding decrease in the serum albumin.

It has also long been noted that in bloods in which there is a marked leucocytosis the sedimentation is commonly much accelerated.

In any investigation on sedimentation one must naturally take into consideration the well-established law of physicists known as Stokes's law, according to which the speed of sedimentation, V , is directly proportional to F , the force of gravity, and inversely proportional to η , the viscosity of the dispersion medium, as well as to r , the radius of the particle in accordance with the formula $V = F/6\pi\eta r$.

It will readily be appreciated that one or more of these factors may be much

altered in different disease conditions. Thus in anaemia of the Addisonian type it is obvious that r , the radius of the sedimenting particle or red-blood cell, is very considerably altered, and consequently F also will be affected, whilst again in anaemias of the chlorotic type where the haemoglobin is much reduced and the plasma, according to Lorrain Smith, is much increased, it is reasonable to expect that the viscosity of that medium will be considerably altered, as also will the force of gravity, F , of the cells. Again, it is reasonable to suppose that the factors F , η , and r may, in certain disease conditions, be altered in such proportions as to materially affect V but little. It will be seen, therefore, that the problem of determining the factor or factors underlying the speed of sedimentation of blood is an extremely complex one and probably dependent on a mixture of physical and chemical factors. In order to test some of the theories put forward as to the cause of the rapid sedimentation of red cells in certain diseases various tests and investigations were carried out.

Author's Investigations.

Firstly, with regard to the cause being a matter of hypercholesterolaemia, careful observations by Myers's method on the cholesterol value of both plasma and corpuscles were carried out in fifteen cases. Of these fifteen cases thirteen showed a rapid sedimentation-rate, whilst two of the cases fell within the normal range. In only one instance, and that a case of cholecystitis with gall-stones (a condition in which one would anticipate finding an increase), was there any increase in the cholesterol content of the blood particularly noticeable in the figures obtained for the plasma. All the other cases examined gave practically normal figures, though in the cases of sprue (where the sedimentation-rate is increased) the figures determined were considerably below normal.

Estimations of the fibrinogen content of the blood employing the method of Wu Hsien (13) were undertaken in fourteen cases. Of these cases five showed marked rapidity of sedimentation, whilst the others fell within the normal range. Whipple and Hurwitz (14) state that normally 0.3 to 0.4 gramme of fibrinogen per 100 c.c. of blood is present, and in none of the cases now investigated was the latter figure exceeded.

In order to test further whether fibrinogen played any important part in the phenomenon of sedimentation the plasma from a rapidly sedimenting blood was pipetted off and heated to 59° C. for twenty minutes to coagulate this protein. The plasma was then filtered and again added to the corpuscles, but no difference in the rate of sedimentation was noted.

No investigations as to the proportions of serum albumin and serum globulin were undertaken. Mathews (15) states that there is no method by which a sharp separation of these two bodies can be determined, and therefore it was considered inadvisable to attempt any estimation of the proportions of these two ingredients.

That an increase in the sedimentation-rate is associated with marked leucocytosis is borne out in the majority of cases under review, though exceptions are to be found, and some five cases in which the leucocyte count varied between 12,000 and 20,000 showed no increased rate of sedimentation. That leucocytosis itself is not an essential in the production of increased rapidity of sedimentation is well shown in the cases of sprue and kala-azar, all of which had a definite leucopenia, one case of kala-azar having only 2,000 leucocytes per c.mm., and yet all these cases showed a markedly rapid sedimentation.

As regards the influence of anaemia in the production of rapid sedimentation it was found that all cases investigated in which there was a definite anaemia showed an acceleration of sedimentation. Inasmuch as in all these cases there was some other concurrent disease it was difficult to say how much the sedimentation-rate was affected by the anaemia and how much by the other disease process. The degree of anaemia present seemed to bear a definite relationship to the rate of sedimentation; thus cases showing a very rapid rate of sedimentation were usually associated with a severe degree of anaemia.

Cooper (16), in a discussion following a paper read by him, gave it as his opinion that anaemia does not increase the sedimentation-rate, but it is difficult to think that this is correct in view of the above results and bearing in mind Stokes's law, in which, as shown, certain of the factors concerned must be materially altered.

It is unfortunate that I had not the opportunity of carrying out investigations on cases of chlorosis and Addisonian anaemia, as such would probably have helped to arrive at a more definite opinion on the subject.

It was considered worth while to divide the cases up into their definite blood groups to ascertain if any one group was more prone to rapid sedimentation than another. Adopting the classification of Moss, it was found that of fourteen cases showing rapid sedimentation, four belonged to Group II, two to Group III, and eight to Group IV.

The number investigated is too small to draw definite conclusions, but it would appear that the question of the particular blood group to which the case belongs has no significance in the phenomenon.

In contradistinction to the work of Gilbert and others on cases of leprosy previously referred to, in the one case of the disease which I was able to investigate no acceleration of sedimentation was noted. It is not clear from Gilbert's records whether the cases he worked on were of the nodular or anaesthetic variety of the disease. My case was an early one of the anaesthetic variety, and it may well be that the sedimentation-rate may not be increased in cases of this type, though possibly accelerated in nodular cases, and especially if associated with breaking down of the nodules and ulceration. Moreover, in nodular leprosy there is always some involvement of the liver in the general disease process. Quite recently Landeiro (17) has confirmed this view. In an investigation on fifty cases of the disease he found that in purely anaesthetic cases little or no change was to be found in the sedimentation-rate, whereas in the tuberculous

types a very definite acceleration was noted, the degree of such being dependent on the extent and character of the lesions.

The one factor that seems to emerge from all these tests is that an increased rate of sedimentation is to be expected in those cases where there is some definite derangement of the liver. Such derangement is especially present in cases of kala-azar in which marked involvement of the liver in the disease process is a prominent feature. Again, in sprue, in which the sedimentation-rate is strikingly accelerated, there is undoubted derangement of the liver, and it is a common clinical observation in the early and acuter stages of sprue that the liver is much reduced in size. Moreover, Covell (18), employing the laevulose tolerance test, has shown that in most cases of this disease investigated by him there was a moderate degree of intolerance to this sugar.

In liver abscess, cirrhosis of the liver, cholecystitis, myelogenous leukaemia, and malignant disease affecting the liver, the marked involvement of that organ is obvious. In malaria the liver is practically always the seat of malarial hepatitis, whilst in a generalized infective process, e.g. infective endocarditis, the liver is undoubtedly affected in the general septicaemic process.

If this derangement of the liver results in some defect of the katabolic properties of that organ, it might be suggested that possibly the increased rate of sedimentation noted might be due to some disturbance in the proportions of katabolic substances normally present in the plasma. To this end urea estimations were carried out on three of the most rapidly sedimenting bloods, but no departure from normal in the amount of blood urea was to be noted.

Experiments were also carried out to ascertain, if possible, whether the phenomenon of rapid sedimentation resided particularly in some peculiar property of the plasma or was due to some property of the corpuscles.

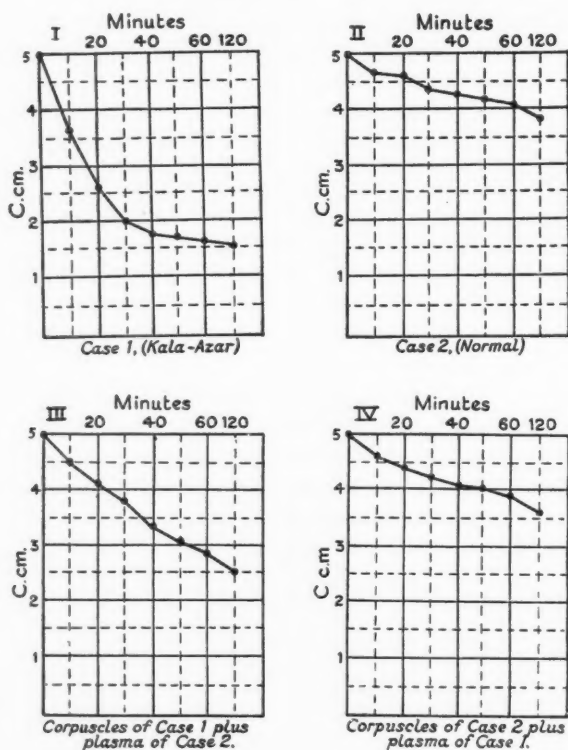
Firstly, the specific gravity of the plasma was determined in nine cases, of which six were normal individuals, whilst the remaining three were cases showing markedly rapid sedimentation, and it was seen that in the latter the specific gravity was quite definitely though moderately exalted.

Next, two cases were taken, one of an individual showing very rapid sedimentation (Case 1), and the other of a normal individual (Case 2). These two bloods were allowed to sediment in the normal way and their rate of settlement noted. The plasma in each case was then pipetted off, and that of Case 2 was added to the corpuscles of Case 1, whilst the plasma of Case 1 was added to the corpuscles of Case 2. Each of the two tubes was then shaken to mix the plasma and corpuscles and the sedimentation-rate again noted. The results are shown in Charts I, II, III, IV.

A study of these will show that the addition of the plasma of the rapidly sedimenting Case 1 to the corpuscles of the normal Case 2 produced practically no difference in the rate of sedimentation, whilst in the other instance in which the corpuscles of the rapidly sedimenting Case 1 were mixed with the plasma of the normal Case 2, a distinctly enhanced rate of sedimentation, though not as precipitous as in the unmixed blood, is to be noted. This would seem to point

to the conclusion that whatever factor is concerned in the production of an abnormal rate of sedimentation, such factor would appear to reside in some property of the corpuscles rather than in any particular change in the plasma.

On the other hand, if the plasma of a rapidly sedimenting blood be removed and replaced by saline, the rate of sedimentation is then found to fall within the normal range. Here, however, one is introducing a very marked change in the conditions. Not only is the specific gravity and viscosity of saline very different to that of plasma, but none of the chemical constituents of plasma other than



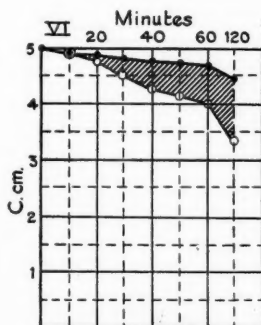
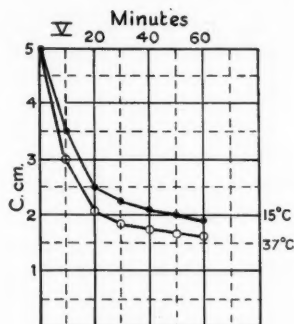
sodium chloride are present, and for those reasons such an experiment seems to offer little elucidation of the cause.

The temperature at which observations are made seems to make a difference, though a slight one, in the rate of sedimentation. To determine this point blood from a case of cirrhosis of the liver was used and allowed to sediment at room temperature ($15^{\circ}\text{C}.$) and also at the temperature of the warm incubator ($37^{\circ}\text{C}.$).

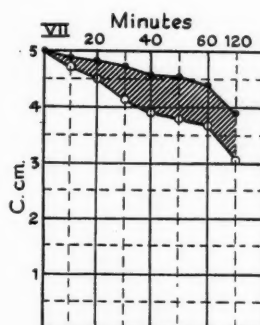
It will be seen (Chart V) that at the higher temperature the sedimentation was slightly more rapid than at the lower temperature, but no very marked change is to be noted. This change may be due to the altered viscosity of the plasma produced by the heating.

A third sample of the same blood was allowed to sediment at a temperature of 9° C., but the rate of settlement was identical with that observed at 15° C.

Seeing that disorder of the functions of the liver seems to play some definite part in the causation of an increased rate of sedimentation, it may well be that a determination of the sedimentation-rate may come to be recognized as a means of testing hepatic efficiency. With that end in view a series of observations are now in progress to see if cases showing an accelerated sedimentation-rate exhibit also a definite intolerance to laevulose. Investigations also on the specific gravity



Normal range of variation
in nine healthy men



Normal range of variation
in nine healthy women

of the red corpuscles and the viscosity of the plasma are to be undertaken, as both of these factors may have a profound bearing on the elucidation of the phenomenon. It is hoped to embody any results obtained in a further communication.

The Normal Standard.

It was only to be anticipated that some variation in the rate of sedimentation was to be expected in normal individuals, and in an endeavour to find out what the normal range of variation was, nine healthy adult males and the same number of healthy females were subjected to examination.

In plotting out the variation the topmost line represents the slowest rate of sedimentation noted, whilst the bottom line represents the most rapid.

The space between represents the normal range of variation. Two charts are appended showing the range of variation in both groups, male and female (Charts VI and VII).

An interesting point brought out is that the normal rate of sedimentation appears to be slightly more rapid in women than in men.

The Cases.

Through the kindness of the physicians attached to the Hospital for Tropical Diseases I have been given opportunities of studying the phenomenon in various cases under their care. These include among instances of tropical affections :

- Sprue (3 cases),
- Amoebic liver abscess (1 case),
- Amoebic dysentery (6 cases),
- Kala-azar (4 cases),
- Subtertian malaria (2 cases),
- Benign tertian malaria (3 cases),
- Ulcerating granuloma (1 case),
- Leprosy (1 case);

and of affections not particularly tropical, cases of :

- Cholecystitis (3 cases),
- Myelogenous leukaemia (1 case),
- Duodenal ulcer (1 case),
- Malignant disease (2 cases),
- Infective endocarditis (1 case),
- Cirrhosis of the liver (2 cases).

Of the tropical affections studied all, with the exception of the case of ulcerating granuloma, four of the cases of amoebic dysentery (the remaining two cases had some complication associated with marked leucocytosis), and the one case of leprosy, show a rate of sedimentation considerably in excess of the normal. Especially is this so in two of the cases of kala-azar (Chart VIII), and to a slightly less extent in the sprue cases (Chart IX), whilst the case of liver abscess (Chart X) shows a rate of sedimentation nearly as dramatic as that associated with the lowest case of kala-azar.

Brief particulars of the cases of these three diseases are appended :

Kala-azar.

Case I. European man. Contracted disease in Soudan. Liver and spleen much enlarged. Fever. Spleen puncture positive. R. B. C. = 3,590,000. White cells = 2,000. Haemoglobin 75 per cent.

Case II. European lady. Contracted disease in India. Typical symptoms of kala-azar. Spleen puncture positive. R. B. C. = 3,000,000. White cells = 2,000. Haemoglobin 50 per cent.

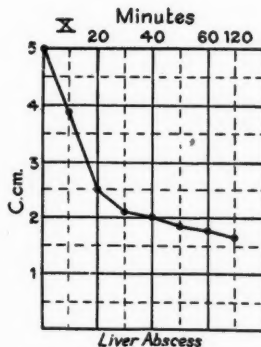
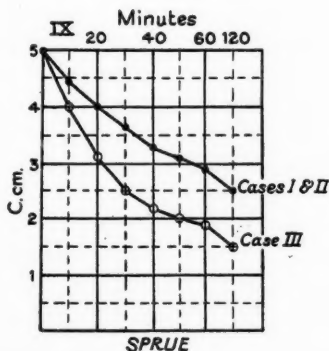
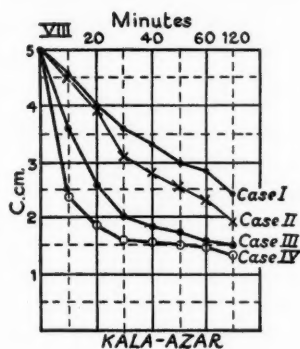
Case III. Native of India. Liver and spleen enlarged. Fever, wasting, cachexia. Spleen puncture showed parasites. R. B. C. = 3,300,000. White cells = 2,000. Haemoglobin 70 per cent.

Case IV. Native of India. Enlarged liver and spleen. Fever, wasting, cachexia. Parasites found in spleen puncture. R. B. C. = 4,200,000. White cells = 2,800. Haemoglobin 80 per cent. Slight poikilocytosis.

Sprue.

Case I. European male. Disease contracted in India in 1924. After three months' treatment recovered and remained well till 1926, when relapse occurred, with pale, copious stools, sore tongue, &c. R. B. C. = 3,560,000. White cells = 5,000. Haemoglobin 75 per cent. Cell changes not marked.

Case II. European male. Disease contracted in India. Several relapses. Now well-marked symptoms and signs of sprue. R. B. C. = 3,000,000. White cells = 5,200. Haemoglobin 70 per cent. Cell changes not marked.

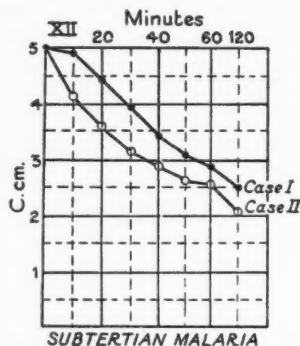
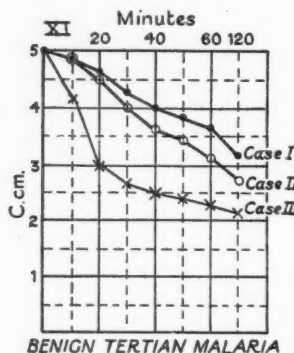


Case III. European lady. Contracted disease in China. First attack ten years ago, with frequent relapses since. Now presents typical signs and symptoms of disease. R. B. C. = 1,300,000. White cells = 3,600. Haemoglobin 40 per cent. Much poikilocytosis and anisocytosis.

Liver abscess.

European male. No previous history of dysentery. New complaining of pain in liver area, fever, &c. Liver much enlarged. Liver aspirated and large amount of pus evacuated, followed by rapid recovery. R. B. C. = 4,100,000. White cells = 26,000. Haemoglobin 80 per cent.

On the other hand, the cases of malaria (Charts XI and XII), although showing a sedimentation-rate outside the normal range of variation, do not present such a rapid or extensive fall as is seen in the three previous charts.



Brief particulars of the cases studied are as follows:

Benign tertian malaria.

Case I. European male. Relapse of malaria with parasites in blood. R. B. C. = 5,000,000. White cells = 6,200. Haemoglobin 90 per cent.

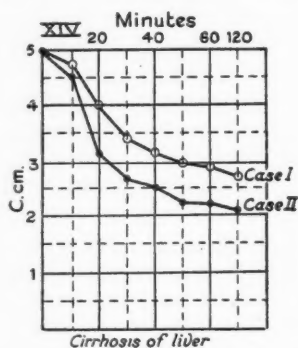
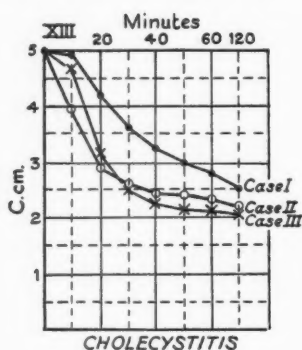
Case II. Native Indian. First recorded attack of malaria. Parasites scanty in blood. R. B. C. = 4,800,000. White cells 3,600. Haemoglobin 80 per cent.

Case III. European male. Relapse of malaria. Parasites in blood. R. B. C. = 4,500,000. White cells = 5,200. Haemoglobin 80 per cent.

Subtertian malaria.

Case I. European male. Relapse of malaria. Parasites in blood. R. B. C. = 4,700,000. White cells = 6,200. Haemoglobin 85 per cent.

Case II. European male. Relapse of malaria with parasites in blood. R. B. C. = 4,600,000. White cells = 5,000. Haemoglobin 80 per cent.



Of the non-tropical cases studied, three were of cholecystitis (Chart XIII), one of myelogenous leukaemia, one of duodenal ulcer, two of malignant disease, one of infective endocarditis, and two were of cirrhosis of the liver (alcoholic) (Chart XIV). All of these, with the exception of the case of duodenal ulcer,

showed a considerably enhanced rate of sedimentation well outside the ordinary normal variation range.

The cases of cholecystitis were quite typical. Case I showed practically a normal blood count, whilst Cases II and III showed a moderate degree of leucocytosis. The two cases of cirrhosis of liver showed the usual signs and symptoms of that disease, and the blood in both instances was practically normal.

The case of duodenal ulcer was extremely interesting. The condition on clinical examination was obscure, the patient chiefly complaining of some pain in the region of the gall-bladder. Blood examination was normal. A provisional diagnosis of gall-bladder trouble was made, but operation revealed a duodenal ulcer, and the gall-bladder was normal.

Seeing that in cases of gall-bladder trouble the rate of sedimentation, as revealed in the charts of cholecystitis, is manifestly markedly increased, it would appear that the sedimentation-test may offer some considerable help in differentiating gall-bladder cases from cases of duodenal ulceration.

Conclusions.

1. The rate of sedimentation of red-blood corpuscles varies markedly in a great variety of disease conditions.

2. Little value can be placed on the sedimentation-test as an aid in differential diagnosis.

3. It would appear that in all cases showing increased rapidity of sedimentation there is some concomitant derangement of the liver.

4. Rapid sedimentation is not dependent in any way on the particular blood group to which the blood belongs.

5. Rapid sedimentation appears to occur in any disease condition associated with anaemia.

6. The cause of the phenomenon does not appear to reside in an increased proportion of fibrinogen in the blood.

7. The property of rapid sedimentation seems to reside in some property of the corpuscles rather than in any particular property of the plasma.

8. It is probable that the phenomenon of rapid sedimentation is due to a combination of both physical and chemical changes.

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THE LIMITATION OF MUSCULAR EFFORT AND ITS RELATION TO CARDIAC FAILURE¹

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With Plates 6 and 7

I. *Introduction.*

A. Physiological. The extent to which the heart is capable of effecting oxygen supply to the working muscles is usually looked upon as the important factor in the limitation of voluntary effort. Thus in Anrep's revised edition of Bainbridge's monograph on muscular exercise (2, p. 140), in the section entitled 'The Limits of Muscular Exertion', we read: 'The possibility that, even during the heaviest work, the respiratory mechanism ever fails to provide in the lungs sufficient oxygen to meet the needs of the body may certainly be dismissed, since the alveolar tension of oxygen, under these conditions, scarcely falls below that present during rest; and the cause of the inadequate supply of oxygen must be sought in the circulatory system.' And in the summary to this section: 'A man's maximum working power is determined, not by the functional capacity of his skeletal muscles, but also by the supply of oxygen to the muscles, heart, and brain. Since the supply of oxygen ultimately depends on the output of the heart, the limit to the exertions of which a man is capable is reached when the output of his heart fails to correspond with the demands of the tissues for oxygen.' A similar view has been expressed by Yandell Henderson (29) in a recent lecture. Hill and Flack believe the heart fails in this respect when the coronary circulation becomes inadequate to maintain the oxygen supply to the myocardium. Bainbridge, however, points out that an alternative explanation is possible; that the coronary circulation is always adequate, while the actual minute volume of which the heart is capable is insufficient to keep the muscles adequately supplied with oxygen during intense exertion. But, in Bainbridge's monograph at least, and, as far as we can see, fairly generally throughout the literature, the limitation of voluntary effort is discussed from the point of view of oxygen supply alone. The possibility that failure of the circulatory and respiratory systems to excrete carbon dioxide might be an important factor in the limitation of effort seems hardly to have been considered.

¹ Received December 20, 1927.

² Preliminary reports have been communicated to the Physiological Society (13, 14).

The work of Fletcher, Hopkins, A. V. Hill, Meyerhof, and others (for a general review of this subject see Hopkins (44, 45)) has shown that the thermochemical changes which occur in isolated muscle on stimulation may be divided into (1) an anaerobic (non-oxidative) contraction phase during which glycogen is converted into lactic acid with the liberation of energy, and (2) an aerobic (oxidative) recovery phase during which one-fifth of the lactic acid formed is oxidized to carbon dioxide and water, and provides the energy necessary for the resynthesis of the remaining four-fifths into glycogen; during continued contraction of muscle both these phases proceed simultaneously. Under complete anaerobic conditions all the lactic acid formed during contraction accumulates, and reacts with the buffer salt (sodium-protein compounds) present in the muscle fibre with the liberation of equivalent quantities of weaker buffer acid. The hydrogen-ion concentration (cH) of the muscle therefore rises slowly to a point at which further production of lactic acid from glycogen ceases; contraction now comes to an end, and the muscle is said to be completely 'fatigued'. The rate at which a muscle can continue to work under partially anaerobic conditions (as in the body) must therefore depend on the rate at which it can continue to liberate lactic acid without lactic acid accumulating, and this must be determined by the rate at which the lactic acid formed can be removed, which in turn depends upon the rate at which oxygen can be supplied. If the work done by the muscle is such that the necessary rate of lactic acid production can be balanced by its oxidative removal, a 'steady state' is arrived at, and contraction at this rate can be continued for a long period (Fletcher, 19). But as soon as the supply of oxygen fails to meet the demand, lactate begins to accumulate, and the hydrogen-ion concentration rises quickly to the point at which further lactic acid production ceases.

Recently Hill, Long, and Lupton (35-40, 20, 53; *vide* also Hill's Oliver-Sharpey Lectures (33) and Herter Lectures (34)) have extended this conception of muscular contraction to the interpretation of the respiratory exchange during exercise. They point out that the oxygen requirement of work can be divided into the excess oxygen intake while the work is in progress (O_2 income), and the excess oxygen that has to be taken in after exercise ceases (O_2 debt) before the oxygen intake per minute returns to its resting level. During moderate muscular exertion there is a slight initial accumulation of lactate in the blood, while the oxygen intake per minute becomes constant at a level below the maximum of which the individual is capable; the oxygen debt incurred is small. They conclude that, during work of this kind, the initial accumulation of lactic acid in the muscles is due to their oxygen supply being at first insufficient to remove it at the rate at which it is formed, but as cardio-respiratory activity works up, the rate of formation of lactic acid becomes balanced by its oxidative removal, and a condition is arrived at comparable with the steady state of contracting isolated muscle described by Fletcher. After the first minute or two, the oxygen requirement can be met out of income, i.e. through the cardio-respiratory system, and the small oxygen debt incurred is due to the initial accumulation of

lactate only. When, however, the work is severe, the oxygen intake rises to a maximum of which the individual is capable, fatigue rapidly ensues, and a very large oxygen debt is incurred; the concentration of lactate in the blood rises progressively, and reaches its maximum only after exercise ceases. Under these circumstances they conclude that the oxygen requirement of the exercise can no longer be met out of income, the oxygen intake representing the maximum of which the individual is capable, so that lactate accumulates progressively, and a large oxygen debt is incurred. Hill, Long, and Lupton (38, p. 135) consider that the limit of muscular effort must be determined by the cerebral distress, consequent on the rise of cH of the blood due to accumulation of lactate, or the result of anoxaemia, when the maximum cardio-respiratory activity of which the body is capable fails to meet the demands of the tissues for oxygen. Again, we fail to find in the most recent work on muscular exercise in man, work in which the maximum of human endurance was particularly considered, any suggestion that the ability of the body to excrete carbon dioxide might be a factor in the limitation of effort.

B. Clinical. In clinical medicine this physiological conception of the limitation of muscular effort has its parallel in Sir James Mackenzie's theory of cardiac failure. Mackenzie (55) supposed that the force inherent in the heart-muscle might be considered to be divided into two parts: a part which is employed to maintain adequate circulation under resting conditions, the 'rest force', and a part which is called into action only when effort is made, the 'reserve force'. When the heart is subjected to any handicap in the performance of its function, such as valvular or myocardial disease, some of the reserve force is used up to supplement the rest force and to maintain adequate circulation under resting conditions. Heart failure thus starts with limitation of effort due to reduction in the reserve force, and when the reserve force is completely exhausted in maintaining adequate circulation under resting conditions, then symptoms of failure, such as oedema, supervene. But the reserve force of a normal heart is also completely used up during the extremes of muscular effort. Thus, writing in his Oxford system, Mackenzie (56) says: 'When a healthy individual undertakes some form of severe bodily exertion—for example, running at the "top of his speed"—there comes a time, sooner or later, when he suffers a temporary exhaustion of his reserve force. Ultimately, on account of this temporary exhaustion, he is compelled to desist.' And again: 'Exhaustion of the reserve force in individuals with enfeebled hearts is of the same nature as exhaustion of the healthy heart, and heart failure in the first instance is simply the premature exhaustion of the reserve force of the heart.' The Mackenzie theory of cardiac failure, as we understand it, makes the mechanism of the limitation of voluntary effort in the normal man identical with the mechanism of heart failure under resting conditions, in the sense that the reserve force is completely exhausted in both cases. In the former it is temporarily used up in attempting to maintain the necessary circulation rate under working conditions, while in the latter it is permanently used up in attempting to maintain adequate circulation under

resting conditions. It is therefore natural to inquire whether the symptomatology of these two conditions is the same, as this theory might at first lead one to suppose. The symptoms of 'decompensated' heart failure, in the sense in which we shall use the word 'decompensated' throughout this paper, as opposed to those of compensated heart disease (limitation of effort alone), are dilatation of the heart, cyanosis, venous engorgement, enlargement of the liver, and oedema of the extremities. Do such symptoms develop during extreme muscular exertion in the normal man?

Routine clinical examination of athletes after violent exertion has seldom been made, largely presumably because their clinical condition does not demand it. Cyanosis is certainly seldom to be observed. Orthodiagraphy seems to have demonstrated that after exercise the size of the heart, instead of being increased as clinicians used to believe, is actually reduced (Lewis (51)), and therefore, if dilatation of the heart during exercise actually occurs, it is probably physiological, in accordance with the demands of Starling's law. Gordon, Levine, and Wilmaers (23) examined competitors immediately after finishing the American Marathon race, and found that their hearts were not enlarged but usually reduced in size, that there were no abnormal physical signs in the lungs, and that the liver edge was not palpable. It might be argued that the symptoms of cardiac failure did not supervene because exertion was not continued for sufficient time to allow them to develop, but the time for the Marathon race is about three hours, while the sudden onset of auricular fibrillation, paroxysmal tachycardia, or coronary thrombosis may lead to symptoms of congestive cardiac failure within an hour. On the other hand, the collapse of the competitors seemed to be of a nervous type, in conformity with the usual teaching that general fatigue is localized within the nervous system; this certainly conforms with our experience. Such is all the direct evidence on the question that we have been able to obtain, and the fact that so little evidence is available strongly suggests that the signs of congestive cardiac failure do not as a rule develop during the extremes of muscular exertion. After all, if they did, it is almost certain that they would have been frequently observed by clinicians, and heart failure following severe exercise would then be regarded as a common though transient clinical condition. We have therefore consulted the standard text-books of clinical medicine, and have obtained, we must confess, but little satisfaction. A few such cases are described by Sir Clifford Allbutt (1) in his article on 'over-stress of the heart' in Allbutt and Rolleston's *System of Medicine*. Gibson (21), in Osler and Macrae's *System*, describes a type of heart failure directly the result of overstress with cyanosis and oedema, indistinguishable from severe cases of mitral regurgitation; no actual cases are quoted. In Mackenzie's Oxford system (56) we can find no mention of this condition. Cowan and Ritchie (16) state that a healthy heart does not suffer dilatation by physical stress, and that cardiac overstrain is very rare in young individuals. Such cases are therefore uncommon, and the modern trend of opinion is to regard those that do occur as transient heart failure, precipitated by excessive muscular exertion, in a heart previously damaged by

infection; to teach that excessive exercise does not damage the healthy heart, and that repeated excessive exercise does not lead to cardiac hypertrophy. Sir Thomas Lewis (51) points out that *the* important cause of heart failure in young people is chronic infection of the myocardium, or the sudden onset of some disorder of the cardiac rhythm with ventricular tachycardia, again frequently the result of infection. In all his cases of actual dilatation of the heart, previously attributed to heart strain, the basal condition proved to be an unrecognized paroxysm of tachycardia. The situation is summed up when he writes:

'The circulatory organs are built to stand the strains which they themselves create; their reserve is often under-estimated; it is the full supply of blood to the muscles which will fail, and not the heart, when the call is excessive. How comes it that in the horse, the most heavily strained beast of burden, chronic heart affections are almost unknown? *A priori* the hypothesis of heart strain is not reasonable. It is linked to the old tradition that the first and last cause of heart failure is a mechanical defect; that tradition is already moribund.'

Our clinical experience, for what it is worth, and the above evidence unsatisfactory though in some respects it is, points definitely to the conclusion that an essential difference exists between the symptoms of extreme muscular exhaustion in the normal man, and those of congestive cardiac failure, under resting conditions, in the patient with organic heart disease. The accumulation of blood on the venous side of the heart, in the lungs, the great veins, and liver, in congestive cardiac failure must be largely due to failure of the heart-muscle to effect the necessary output per minute to keep pace with the resting venous return; probably much more to this than to failure of the cardiac output to maintain the oxygen supply to the tissues, particularly as Peabody (65, 68) has shown that the basal metabolic rate (O_2 consumption) of the body is, if anything, increased in cardiac decompensation, and not decreased as might have been anticipated. On the other hand, the absence of the signs and symptoms of venous congestion after severe exercise in healthy men shows that the normal heart is capable of coping with the enormous venous return of the most intense exertion, and that the symptoms of this condition must be due almost entirely to failure of the ventricles to effect the necessary blood-supply to the tissues, and little, if at all, to failure of the cardiac output to cope with the venous return. This statement is open to criticism on the grounds that it is illogical to separate cardiac output and venous return, as cardiac output is impossible without venous return, and venous return impossible without cardiac output. But the symptomatology of cardiac failure, as compared with that of voluntary effort, shows clearly that a dissociation between venous return and cardiac output can occur, presumably because the rate of venous return depends chiefly on other factors than the transmission of pressure of ventricular origin through the capillary system. The physiological mechanism of the limitation of voluntary effort, and the mechanism of the production of symptoms in cardiac failure, are essentially different, and by the term 'heart failure' the physiologist and the clinician usually mean different things. By heart failure the

physiologist means that the reserve force is completely expended in maintaining the increased blood-flow necessary to effect the required oxygen supply to the working muscles. By heart failure the clinician means that the reserve force of the heart is completely used up in coping with the venous return under resting conditions.

But heart disease is usually a slow process, and as it advances the functional capacity of the heart-muscle to effect the circulation of the blood is progressively reduced, as shown by the gradual reduction in the patient's capacity to work. During the gradual transition from the onset of cardiac disease to death by cardiac failure, for far the greater part of the time, and even at a stage when the patient's capacity to do work is greatly reduced, the symptoms of cardiac failure not only remain absent at rest, but do not supervene even on attempted effort. But eventually, with the progress of the disease, the reserve force of the heart is completely exhausted, and compensation passes over into decompensation; in our experience this transition is usually relatively abrupt even in cases failing with normal cardiac rhythm. Symptoms of venous congestion are now present at rest, or supervene very easily on the least exertion, and if the cause of the condition is untreated or untreatable, failure progresses rapidly to a fatal issue. It is in the functional pathology of this transition that we are interested, in the mechanism of the limitation of effort in the normal man, and its relation to the mechanism of the limitation of effort in the compensated cardiac patient, and then again in the relationship of this to that of congestive cardiac failure.

In 1924 one of us (A. E. C.-K.), in conjunction with Dr. Arthur Maitland Jones, started to determine the maximum oxygen intake in patients with compensated rheumatic heart disease, with the idea that this would afford a numerical measurement of the degree of cardiac efficiency of our patients. But early in this work, which was too incomplete for publication, we became impressed by the fact that as the rate of work was increased in any one patient, the percentage of carbon dioxide in the expired air fell off, due presumably to a decrease in the CO_2 -carrying power of the blood consequent on the accumulation of lactate. It then occurred to us that perhaps the ability to excrete carbon dioxide might be an important factor in the limitation of voluntary effort, in which case the capacity to effect pulmonary ventilation might be a more important factor in the limitation of effort than was commonly supposed. We therefore thought it worth while to reinvestigate the respiratory exchange during muscular effort from this point of view, before proceeding farther with a study of the functional pathology of heart disease. The results of this investigation, the conclusions we have arrived at as to the mechanism of the limitation of effort in the normal man, and their possible bearing on the clinical problem we have just attempted to outline, are reported in this paper.

II. Experimental Methods.

The respiratory exchange has been investigated in five normal students during work of increasing degrees of severity. In three (Subjects 3, 4, and 5) the effect of breathing 26 per cent. and 16 per cent. oxygen on the respiratory exchange during work was also studied, and in two (Subjects 3, 4) the effect of breathing 5 per cent. carbon dioxide. The object of these experiments has been to investigate the mechanism of the limitation of voluntary effort in the normal man, and to see what relationship this bears to the functional pathology of cardiac failure. Rates of work have therefore been selected which would practically completely exhaust the average normal young man in five to ten minutes, as limitation of effort of this kind is said to depend on failure of the heart to maintain the blood-supply to the muscles. As we were not concerned with the mechanical efficiency of the individual, we decided not to use a bicycle ergometer, but to make our subjects do 'standing running' at increasing rates, the method employed by Hill, Long, and Lupton in their investigations. Standing running has a considerable advantage over pedalling an ergometer. Firstly, greater rates of work can be investigated more easily; secondly, this kind of work is physiologically natural, the kind for which man is designed; while thirdly, it permits of natural and free breathing, which pedalling a bicycle ergometer, on account of the strain which it throws upon the arms and the accessory muscles of respiration, does not. The disadvantage of exercise of this kind is that the amount of external work done cannot be actually measured, and it is difficult to ensure that the subject maintains the same rate of work (as distinct from the rate of running) throughout one experiment; moreover, he is apt to compensate unconsciously for increased speed of running in successive experiments by decreased leg-lift, in spite of instructions to the contrary. This, however, we have been on the look-out for, and the subject was informed whenever he seemed to be 'slacking' in this way. In Subjects 1 and 2, who were both indifferent runners, the rate of running was increased in successive experiments, until complete exhaustion was produced while an experiment was still in progress. These experiments are not therefore directly comparable, as in successive experiments both the rate of work and the duration of the work altered. These subjects, too, had no particular experience of running and failed to maintain their rate of work constant, or slacked off as distress supervened. Later it was found more satisfactory to employ subjects with some aptitude for and experience of long distance running, and to keep the duration of each experiment the same (8 minutes); successive experiments on each of these subjects are directly comparable. We must emphasize particularly that in all our experiments the rate of work demanded of our subjects was severe and not far removed from the maximum of which they were capable; mild or even moderate exertion has not been investigated.

General technique. Subjects 1, 2, and 3 came at the same time each morning after an ordinary breakfast, but Subjects 4 and 5, on whom determinations of oxygen debt at the end of exercise were made, came at 8 a.m. in a post-absorptive condition, having taken no food since an ordinary dinner on the previous evening. The Douglas bag technique has been used in all experiments in much the same way as by Hill, Long, and Lupton (37). The subject breathed through Rosling rubber valves (supplied by Messrs. Siebe, Gorman & Co.), and before each experiment these valves were tested for leaks both during quiet and forced breathing, the side tubes fitted to the valve box for the collection of alveolar air, as described below, making testing for leaks easy. Subjects 1 and 2 breathed from the outside air, and Subjects 3, 4, and 5, on whom experiments breathing gas mixtures were performed, out of a large Douglas bag of 1,600 litres capacity, even when they were breathing ordinary air, so that the experimental conditions might always be the same, and the subject kept in complete ignorance

of the nature of the gas mixture he was breathing. The big Douglas bag was fitted with a water manometer and supported by adjustable strings, so that all gas mixtures in it could be kept at the prevailing barometric pressure. The expired air passed down a metal tube fitted with three 3-way aluminium taps, to the side tubes of which Douglas bags could be quickly attached as required; the subject's expired air could thus be collected over any time interval desired. The general arrangement of our apparatus (supplied by Mr. H. E. Kendrick, 342 St. John's Street, E.) is shown in Pl. 6, Figs. 1 and 2. Before any experiment was commenced, the subject rested, reclining in a 'deck-chair', for at least five minutes. The resting respiratory exchange was then determined by turning the subject on to the first of the Douglas bags, and collecting all the expired air over a measured period of five to ten minutes. The subject then stood up, and on receiving the command commenced vigorous standing running to a metronome set at a certain speed, while the expired air was collected into separate Douglas bags during *each* successive minute by turning the necessary taps at exact minute intervals without attention being paid to the phases of the subject's breathing. In our early experiments the respiration rate was counted by watching the swellings of the Douglas bag, but in our later experiments more accurately by watching the lever actuated by the tambour of the alveolar air apparatus. As soon as this part of the experiment was over, samples were quickly taken out of the bags into sample bottles (see Pl. 7, Fig. 3) similar to those used by McCann and Hannon (54). These were filled with a mixture of equal parts of glycerine and pure saturated sodium chloride solution, a mixture which when fresh does not absorb appreciable quantities of carbon dioxide over a period of twelve hours, but which when old may do so slightly, probably on account of contamination with saliva; this mixture was therefore renewed at frequent intervals. These samples were subsequently analysed on Haldane-Henderson burettes within twelve hours. Except in some of the very long experiments, in which analysis of alveolar air samples had to be made as well, analysis of samples was always performed in duplicate, and when agreement was not obtained, a third analysis was undertaken. The volume of expired air in the Douglas bags was measured by emptying them into a gasometer measuring to the nearest 100 c.c.; the temperature of the air in the gasometer was taken to be the average of the temperatures at the top and at the inlet. The actual time taken to complete an experiment varied from eight to twelve hours, and every experiment was finished on the same day as it was begun.

When the oxygen debt was to be recorded, on the cessation of work, the subject immediately sat down, and the whole of his expired air was collected for exactly half an hour into a large bag. At the end of this period a sample was taken out of this bag, and the volume of air in the bag measured in the ordinary way. In determining the magnitude of the oxygen debt it is theoretically necessary to follow the recovery process to completion, that is for an hour or more. This is seldom practicable, but Hill, Long, and Lupton (37) have shown that, if the recovery period is followed for half an hour, and the initial resting metabolism of the subject employed as base line, results are obtained which are not far from the truth. There is a small remainder of excess oxygen intake after this which is not included, and so the debt determined over a period of half an hour alone is a little too small. But the resting metabolic rate after exercise is temporarily elevated, so if the initial oxygen consumption is used as a base line instead of the final oxygen consumption, which is theoretically incorrect, but all that can be done if recovery is only followed for half an hour, the oxygen debt calculated in this way is a little too great. But these two errors are opposite in direction, and in practice approximately cancel out.

Technique breathing gas mixtures. These mixtures were made up by mixing approximate volumes of cylinder oxygen, nitrogen, or carbon dioxide, with appropriate volumes of ordinary air in a large gasometer, and transferring

the contents of the gasometer to the large Douglas bag. The exact composition of the mixture was subsequently determined by analysis, samples for this purpose being withdrawn from the big bag immediately after cessation of exercise. When the recovery period was followed, the subject continued to breathe the same gas mixture, except in the case of carbon dioxide mixtures, when the subject was turned on to air on the cessation of exercise. Preliminary experiments showed that an oxygen-nitrogen mixture stored in the large bag would keep constant for at least an hour, and a carbon dioxide mixture for at least ten minutes. Before every experiment breathing a gas mixture, the resting metabolism of the subject was first determined breathing air. The subject was then turned on to the gas mixture, and sufficient time allowed for the oxygen and nitrogen in the blood and body fluids to come into equilibrium with the new oxygen and nitrogen partial pressures in the mixture breathed. As the calculation of the volume of oxygen absorbed by the subject depends on the percentage of nitrogen and percentage of oxygen in the expired air, it is exceedingly important to allow a sufficient equilibration period. For Subject 3 ten, and for Subjects 4 and 5 fifteen, minutes were allowed. The resting metabolism of the subject was now again determined by collecting the expired air over a period of five to ten minutes; the total equilibration periods therefore, before exercise commenced, were at least fifteen and twenty minutes respectively. The resting respiratory exchanges of our subjects, determined while they were breathing air, and then determined again after being equilibrated with other oxygen-nitrogen mixtures, are shown in Tables I and II.

It is apparent that in many of our experiments equilibrium had actually been established, but that in a few equilibrium had not quite been arrived at. This question of equilibration with gas mixtures is fully discussed by Hill, Long, and Lupton (37), and it is clear from their conclusions that the period for equilibration we allowed should have been ample, in view of the fact that the rise or fall of oxygen partial pressure, above or below that of air, that we have had to allow for has been comparatively small. Moreover, as they point out, although incomplete equilibration may introduce a slight error into the determination of the respiratory exchange at rest, this small error will vanish completely when the oxygen consumption rises to that of hard muscular work. The equilibration periods that have been allowed are therefore sufficient for the accurate determination of the respiratory exchange during work, but, as they may not have been quite long enough for the accurate determination of the respiratory exchange under resting conditions when oxygen-nitrogen mixtures were breathed, such determinations had not been used in the calculation of the oxygen debt. Hill, Long, and Lupton (37) have also come to the conclusion that breathing low oxygen pressures within limits does not seriously retard the speed of the recovery process after exercise. Half an hour has therefore been taken to be a sufficient period to allow for the approximate determination of the oxygen debt after exercise when 16 per cent. oxygen is breathed.

Collection of alveolar air during exercise. The alveolar air was collected during work in Subjects 4 and 5. Henderson and Haggard (32) have described an automatic method of obtaining the alveolar air during exercise, based on the Krogh and Lindhard (48) principle. The inspiratory force is employed to draw over some of the last of the expired air of the last breath, and gradually displaces ordinary air from a sample tube. As collection of samples by this method requires some time, a modification of this method has been devised by which we could collect samples of the alveolar air every minute in succession during exercise. A sample bottle is completely filled with glycerine mixture, and connected through an electro-magnetic tap by flexible tubing to a metal tube inserted just outside the expiratory valve, and the side tube of the sample bottle is arranged so that siphonage occurs as soon as the electro-magnetic tap opens. The space between the inspiratory and expiratory valves is similarly

TABLE I.

Subject No.	Experiment No.	Gas Mixture breathed.	Pulmonary Ventilation. Litres.	Respiration Rate.	O ₂ absorbed. c.c. per Minute.	CO ₂ excreted. c.c. per Minute.	R. Q.	% O ₂ absorbed.	% CO ₂ excreted.	Alveolar O ₂ %.	Alveolar CO ₂ %.
3	5	Air	6.93	12	271	236	0.87	4.51	3.93	—	—
		26 % O ₂	6.32	12	277	213	0.77	5.05	3.89	—	—
	6	Air	9.29	13	319	297	0.93	3.96	3.69	—	—
		26 % O ₂	7.48	14	287	232	0.81	4.42	3.57	—	—
	4	Air	6.07	14	246	197	0.80	4.69	3.76	7.00	5.66
		26 % O ₂	6.24	13	258	197	0.77	4.80	3.67	6.69	5.71
4	5	Air	6.39	11	247	219	0.89	4.50	3.99	6.19	5.75
		26 % O ₂	6.03	10	246	212	0.86	4.74	4.09	6.38	5.73
	5	Air	8.19	18	234	217	0.93	3.34	3.10	6.16	5.21
		26 % O ₂	7.34	17	252	208	0.83	4.02	3.31	7.06	5.63

The resting respiratory exchange of Subjects Nos. 3, 4, and 5 determined while breathing air, and then again while breathing 26 per cent. oxygen, after an equilibrium period of 10 minutes for Subject No. 3, and 15 minutes for Subjects Nos. 4 and 5.

TABLE II.

Subject No.	Experiment No.	Gas Mixture breathed.	Pulmonary Ventilation. Litres.	Respiration Rate.	O ₂ absorbed. c.c. per Minute.	CO ₂ excreted. c.c. per Minute.	R. Q.	% O ₂ absorbed.	% CO ₂ excreted.	Alveolar O ₂ %.	Alveolar CO ₂ %.
3	7	Air	8.50	18	298	275	0.92	4.02	3.71	—	—
		16 % O ₂	8.52	19	314	275	0.87	4.22	3.69	—	—
	8	Air	7.48	15	283	242	0.85	4.33	3.70	—	—
		16 % O ₂	7.16	13	277	246	0.89	4.43	3.94	—	—
	4	Air	6.64	13	255	216	0.85	4.45	3.78	6.24	5.72
		16 % O ₂	6.39	13	226	205	0.91	4.11	3.73	6.13	5.60
4	7	Air	7.67	10	261	262	1.00	4.00	4.02	—	—
		16 % O ₂	6.12	12	242	210	0.87	4.65	4.05	6.47	5.60
	5	Air	7.25	18	241	193	0.80	3.82	3.05	6.45	5.37
		16 % O ₂	7.92	16	244	226	0.93	3.54	3.28	5.43	5.06
	6	Air	7.75	13	251	233	0.93	3.80	3.53	6.10	5.39
		16 % O ₂	7.72	14	266	226	0.85	4.04	3.43	6.38	5.29

The respiratory exchange of Subjects Nos. 3, 4, and 5 determined while breathing air, and then again while breathing 16 per cent. oxygen, after an equilibrium period of 10 minutes for Subject No. 3, and 15 minutes for Subjects Nos. 4 and 5.

connected by small diameter flexible tubing to a tambour, which operates a lever along which a current passes, and this dips into a mercury cup placed in the circuit. During inspiration the movement of the lever makes a contact, opening the electro-magnetic tap, which allows siphonage to occur, with the result that a few c.c. of the last part of the last expired breath is drawn into the bottle; but as soon as expiration starts again, the contact is broken and siphonage stops. By this method a 200 c.c. sample is easily collected during work in a minute, and a similar sample in two or three minutes during rest. By attaching a number of sample bottles to the electro-magnetic tap the alveolar air can be collected separately during work over a number of successive minutes. The details of this apparatus are shown in Pl. 7, Fig. 3, and its general arrangement in Fig. 4.

The composition of the alveolar air is continuously fluctuating; in respect of CO_2 it is maximal at the end of expiration and minimal at the end of inspiration. These fluctuations under resting conditions are slight, but during work they may be great. The results obtained by the Krogh-Lindhard method, under resting conditions, are apt to be low in respect in CO_2 and high in respect of O_2 , as the volume of the tidal air is frequently too small to wash out completely the dead space of the apparatus with alveolar air. On the other hand, during work, the volume of the tidal air is ample for this purpose, but the alveolar air is being collected at the end of expiration only. The results obtained by our method are therefore likely to be too high in respect of CO_2 , and too low in respect of O_2 , in comparison with the real *average* composition of the alveolar air during muscular exercise. We do not claim that the composition of the alveolar air collected by this method represents the true average composition of the alveolar air throughout the respiratory cycle, but we do claim that the average composition of the alveolar air must be somewhere between that of the alveolar air collected by this method and that of the expired air over the same time interval. The degree of consistency attained by our method of collecting the alveolar air under resting conditions is seen by reference to Tables III and VI.

Calculation of results. The results of our experiments have been calculated in the ordinary way. The volume of the inspired air has not been directly determined, but calculated from the percentages of nitrogen in the expired and inspired airs respectively. The difference between the actual volume of expired air corresponding to any volume of inspired air is always so small, even when the respiratory quotient is high, that it makes no appreciable difference whether the percentage of oxygen absorbed or carbon dioxide excreted is calculated in terms of inspired or expired air. We shall therefore speak throughout of pulmonary ventilation, and not of inspired or expired air specifically, the volume difference between them being negligible. Pulmonary ventilation, tidal air, dead space, and vital capacity are expressed in litres or c.c. of moist air at prevailing barometric pressure, but reduced to body temperature ($37^\circ\text{C}.$); oxygen intake, carbon dioxide output, oxygen debt, and oxygen requirement, however, in volumes of dry gas at N.T.P. As all our gas mixtures breathed were at prevailing barometric pressure, percentages and pressures are interchangeable; for convenience we shall refer to percentages throughout.

The oxygen debt has been calculated for each experiment, not from the resting metabolism for that experiment, but from the average value of all the resting post-absorptive determinations for the particular individual. This method is judged to be more accurate, as any slight error in the determination of the resting metabolism would grossly affect the calculation of the oxygen debt over a period of half an hour. For this reason, and also for the reasons already given, determinations of the resting oxygen consumption when gas mixtures other than air were breathed have been neglected, and the debt in these experiments calculated from the average of all the basal determinations made on the subject when he was breathing air. Schneider (79, 81) has produced evidence to show

that the resting oxygen consumption of the body is reduced by fall of barometric pressure below 410 mm. Hg (10,000 ft.), but as 16 per cent. oxygen at prevailing barometric pressure corresponds to a total barometric pressure of 580 mm. Hg (7,000 ft.), this effect does not enter into our experiments. Douglas and Haldane (18) have shown that during exercise the dead space both for oxygen and carbon dioxide increases considerably, and that the O_2 dead space increases more than the CO_2 dead space; Haldane (26) therefore regarded the dead space as a functional entity. Krogh and Lindhard (47, 48, 49), Pearce (69, 70), and Pearce and Hoover (71), however, maintain that the dead space is anatomically determined, and that it only increases slightly during exercise. In view of this controversy, we have thought it worth while to calculate our dead spaces in Subjects 4 and 5 from the simultaneous composition of the alveolar and expired air. But we do not claim that the composition of the alveolar air, as determined by our method during work, represents the true average composition of the alveolar air. The results of these calculations are therefore given for what they are worth, but as they were based on a technical method which is at present open to criticism, we do not propose to discuss them or draw any conclusions from them. The dead space has been calculated from the following formulae:

$$CO_2 \text{ dead space} = \text{tidal air} \times \frac{\text{per cent. } CO_2 \text{ alv. air} - \text{per cent. } CO_2 \text{ exp. air}}{\text{per cent. } CO_2 \text{ alv. air}}$$

$$O_2 \text{ dead space} = \text{tidal air} \times \frac{\text{per cent. } O_2 \text{ exp. air} - \text{per cent. } O_2 \text{ alv. air}}{\text{per cent. insp. air} - \text{per cent. } O_2 \text{ alv. air}}$$

The ratio of the O_2 dead space to the CO_2 dead space we have called the 'dead space ratio'.

Explanation of diagrams. All our experiments are set out in a graphic form, and the necessity for the publication of complete protocols is thus avoided. In these graphs time in minutes is represented horizontally. From below upwards in succession, plotted against time, will be found:

(1) The oxygen intake and carbon dioxide output per minute. These volumes are shown as lightly shaded rectangles; a white rectangle surmounting one of these shaded rectangles shows excess O_2 intake over CO_2 output ($R. Q. < 1$), and a black rectangle excess CO_2 output over O_2 intake ($R. Q. > 1$). (2) The respiratory quotient. (3) The percentage oxygen absorption, i. e. the number of c.c. of O_2 taken out of each 100 c.c. of inspired air. (4) The percentage carbon dioxide excretion, i. e. the number of c.c. of CO_2 added to each 100 c.c. of air inspired. (5) The pulmonary ventilation per minute in litres. (6) The respiration rate per minute, either as a curve or in figures.

To make the alveolar oxygen percentage curves in the oxygen-nitrogen mixture experiments comparable with the air experiments, we have plotted in every case the difference between the O_2 percentage in the inspired air and the O_2 percentage in the alveolar air, instead of the actual alveolar O_2 percentage itself; these values are plotted from above downwards, so that a rise in the curve corresponds to rise in the alveolar O_2 pressure. Similarly, in the experiments in which 5 per cent. carbon dioxide was breathed we have plotted the difference between the CO_2 percentage in the alveolar air and the CO_2 percentage in the inspired air, instead of the actual alveolar CO_2 percentage. In the graphs, with the exception of those of experiments in which 5 per cent. carbon dioxide was breathed, all curves are shown rising or falling from their previously determined resting levels while the subject was breathing air; for reasons already given, the determinations of the resting respiratory exchange breathing oxygen-nitrogen mixtures have been neglected. The effect of breathing 5 per cent. carbon dioxide on the respiratory exchange at rest is, however, definite; in these experiments the curves are shown rising or falling from their resting values when the mixture was being breathed.

As already pointed out, the rate of running is not a certain indication of the amount of work done by the subject, and in the same subject experiments at the same rate of running, breathing different gas mixtures, are not quite comparable. In order to compare one experiment with another, we have therefore calculated for the whole duration, or for part of one experiment, the total volume of ventilation, the total amount of oxygen absorbed, and the total amount of carbon dioxide excreted. From these figures we have calculated the average oxygen intake, carbon dioxide output, and pulmonary ventilation per minute, and the 'total' respiratory quotient, percentage oxygen absorption, and percentage carbon dioxide excretion for the whole experiment or particular part of it to be considered; these quantities will be referred to as 'totals' for the sake of brevity. These 'totals' have been plotted against the average oxygen consumption per minute in Subjects 1, 2, and 3, as an approximate measure of the work done in each experiment, and against the total oxygen requirement of the work done in Subjects 4 and 5. In all these figures experiments breathing air are shown as black dots, 26 per cent. oxygen as circles, 16 per cent. oxygen as stars, and 5 per cent. carbon dioxide as squares.

III. Description of Experiments.

Subject No. 1. Student, aged 26. Height 174 cm. Weight 73 kg. Vital capacity 4,910 c.c. Average athletic capacity. Played in the scrum for the Hospital Rugby XV. No particular ability or experience in running.

Five experiments were performed on this subject at increasing rates of standing running (Fig. 5). In Experiments 1, 2, and 3 he was ordered to stop running after ten minutes, and in Experiment 4 after six minutes, but in Experiment 5 he stopped of his own accord, completely exhausted after five minutes of running at 220 steps per minute. In Fig. 6 the 'totals' (*vide* above) for the first five minutes of each experiment (the total duration of Experiment 5) are plotted against the average O_2 consumption per minute during that time.

Subject No. 2. Student, aged 23. Height 181 cm. Weight 73 kg. Vital capacity 4,470 c.c. Tall and lightly built. Has rowed, but does not now take any regular exercise.

Five experiments were performed on this subject at increasing rates of standing running (Fig. 7). In Experiments 1, 2, 3, and 4 he was ordered to stop at the end of 10, 10, 7, and 8 minutes respectively, but in Experiment 5 he stopped of his own accord, completely exhausted after five minutes of standing running at 220 steps per minute. In Fig. 8 the 'totals' for the first five minutes of each of these experiments (the total duration of Experiment 5) are plotted against the average O_2 intake per minute for that part of the experiment.

Subject No. 3. Student, aged 22. Height 172 cm. Weight 60 kg. Vital capacity 4,160 c.c. Lightly built. A keen cross-country runner of average ability.

Nine experiments were performed on this subject. The duration of the work period in each experiment was eight minutes, but the respiratory exchange during the first two minutes of each experiment was not recorded. Four experiments were performed at increasing rates of running breathing air (Fig. 9), but even when running at 220 steps per minute for eight minutes he was not completely exhausted at the end of that period. Two experiments were performed breathing approximately 26 per cent. O_2 , one running at 200 steps per minute (Exp. 5, Fig. 10) and one at 220 steps per minute (Exp. 6, Fig. 11); in the figures referred to these experiments are shown graphically to the left of the corresponding experiments at the same rate of running breathing air. In both experiments the

subject commented on how easy the work seemed. Two experiments were also performed breathing approximately 16 per cent. O_2 , one running at 200 (Exp. 7, Fig. 10) and one at 220 steps per minute (Exp. 8, Fig. 11); in the figures referred to these experiments are shown graphically to the right of the corresponding experiments breathing air. In both experiments the subject commented on the fact that the work seemed 'harder than usual', and during it he became slightly cyanosed. One experiment (Exp. 9) was performed breathing 5 per cent. CO_2 , and running at 200 steps per minute; this experiment is shown graphically in Fig. 12 to the right of the corresponding experiment breathing air. As is to be expected, the pulmonary ventilation at rest breathing the mixture is much greater, and the percentage oxygen absorption and percentage CO_2 excretion much less, than when breathing air; the respiratory quotient was 0.80; the equilibration period allowed was twenty minutes. During the running he became very white, ran in bad style, and afterwards said that he felt 'beastly', and that it had given him a headache. In Fig. 13 the 'totals', calculated for each of these experiments, are plotted against the average O_2 consumption per minute of that experiment.

Subject No. 4. Student, aged 22. Height 175 cm. Weight 65 kg. Vital capacity 4,510 c.c. Lightly built. Ran cross-country for Cambridge University.

Nine experiments were performed on this subject; the duration of each experiment was eight minutes, and the 'alveolar air' was collected during each of the last six minutes. His resting metabolism breathing air before each experiment is shown in Table III, and the O_2 requirement, O_2 debt, and O_2 income for each experiment in Table IV.

Four experiments were performed at increasing rates of running breathing air (Exps. 1-4, Fig. 14), and at the highest rate of running (220 steps per minute) he finished very exhausted. Two experiments were performed breathing approximately 26 per cent. O_2 , one running at 200 steps per minute (Exp. 5, Fig. 15) and one at 220 (Exp. 6, Fig. 16); in the figures referred to these experiments are shown graphically to the left of the corresponding experiments at the same rates of running breathing air. This subject seemed to notice breathing the high O_2 mixture less than Subject 3. Two experiments were performed breathing approximately 16 per cent. O_2 , one running at 200 steps per minute (Exp. 7, Fig. 15) and one at 220 (Exp. 8, Fig. 16); in the figures referred to these experiments are shown graphically to the right of the corresponding experiments running at the same rate while breathing air. This subject noticed the effect of breathing low O_2 percentages, became definitely cyanosed, and at the end of Experiment 8 was completely exhausted. One experiment (Exp. 9) was performed breathing approximately 5 per cent. CO_2 , and running at 200 steps per minute; this experiment is shown graphically in Fig. 17 to the right of the corresponding experiment breathing air. The equilibration period allowed was ten minutes. During the actual experiment he ran in bad style and became very white, so much so that it required some courage to carry the experiment to its completion. Questioned afterwards he said that it had felt horrid at first (headache and nausea), but after the first few minutes his consciousness became dulled so that he carried on quite mechanically, the lapse of time seeming rapid. He did not complain of any particular respiratory distress.

In Fig. 18 the 'totals' for the work period in all experiments are plotted against the corresponding O_2 requirement of the work done in each experiment. Unfortunately in Experiments 2 and 3, through technical errors, the O_2 debts were not determined, and it is therefore impossible to plot the totals for these experiments against the requirement. In Fig. 19 the percentage of O_2 requirement met out of income, the percentage O_2 absorption, the percentage CO_2 excretion, and the pulmonary ventilation over the half-hour following the cessation of work in each experiment, are plotted against the O_2 requirement of the work done in that experiment. In Experiment 9, when 5 per cent. CO_2 is

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breathed, the capacity of our apparatus did not allow us to follow the recovery period, breathing the same mixture, and on stopping work the subject was immediately switched on to air. The sudden though slight consequent alterations of partial pressure of oxygen and nitrogen in the blood may have affected the calculation of the O_2 consumption during this period, but Fig. 19 shows that the percentage of O_2 requirement incurred as income in this experiment is sufficiently reduced to justify the conclusion that, when breathing CO_2 , the subject incurred a debt which was relatively larger than when breathing air.

TABLE III.

Experiment No.	Pulmonary Ventilation. Litres per Minute.	Respiration Rate.	Tidal Air. c.c.	O_2 absorbed. c.c. per Minute.	CO_2 excreted. c.c. per Minute.	R. Q.	% O_2 absorbed.	% CO_2 excreted.	Alveolar O_2 %.	Alveolar CO_2 %.
1	6.05	15	403	214*	167*	0.78	4.13	3.22	6.70	5.77
2	6.76	13.5	501	252	211	0.84	4.37	3.67	6.40	5.71
3	6.71	14	479	235	209	0.89	4.08	3.63	6.23	5.49
4	5.70	10	570	248	203	0.82	5.05	4.14	6.74	5.81
5	6.07	14	434	246	197	0.80	4.69	3.76	6.69	5.66
6	6.39	11	581	247	219	0.89	4.50	3.99	6.19	5.75
7	6.64	13	532	255	216	0.85	4.45	3.78	6.24	5.72
8	7.67	10	767	261	262*	1.00	4.00	4.02	—	—
9	6.64	9.5	699	249	229	0.92	4.36	4.01	6.54	5.45
Aver.	6.52	12	552	249	212	0.87	4.40	3.80	6.47	5.67

The resting respiratory exchange (post-absorptive) in all experiments on Subject No. 4. Starred values have been neglected in the calculation of averages as being probable errors, or due to over-breathing at rest.

TABLE IV.

Experiment No.	Rate of Running. Steps per Minute.	Gas Mixture breathed.	O_2 Income. Litres.	O_2 Debt. Litres.	O_2 Requirement. Litres.	% of Requirement as Income.	% of Requirement as Debt.
1	168	Air O_2 20.93 %	16.38	4.31	20.69	79.2	20.8
4	220	Air O_2 20.93 %	18.20	5.55	23.75	76.6	23.4
5	200	O_2 25.76 %	18.98	5.25	24.23	78.3	21.7
6	220	O_2 25.79 %	19.09	6.95	26.04	73.3	26.7
7	200	O_2 15.92 %	15.81	5.25	21.06	75.1	24.9
8	220	O_2 15.30 %	15.34	6.50	21.84	70.2	29.8
9	200	O_2 19.96 % CO_2 4.86 %	16.24	5.20	21.44	75.75	24.25

Oxygen income, debt, and requirement in all experiments on Subject No. 4.

The average volume of the tidal air has been calculated for the last six minutes of work in each experiment. The volume of the tidal air, O_2 dead space, CO_2 dead space, and the dead space ratio have been calculated for each minute of work from the third to the seventh inclusive; the eighth minute being neglected on account of the observed tendency of this subject (and others) to decrease the ventilation during the last minute of work, probably with the anticipation of stopping. As our method of recording respiration simply by counting is not very accurate, the calculated volumes for each separate minute

have been neglected, and the average volumes and ratios over this whole period in each experiment are shown in Table V. At rest the O_2 and CO_2 dead spaces are approximately equal, and the dead space ratio (O_2 dead space/ CO_2 dead space) unity. During work breathing all gas mixtures, both the O_2 dead space and the CO_2 dead space increase in volume. During work breathing a high O_2 mixture, and during work breathing a CO_2 mixture, instead of air, the dead space ratio is lowered; the O_2 dead space is relatively smaller, and the CO_2 dead space relatively greater. During work breathing a low O_2 mixture instead of air, the dead space ratio is increased; the O_2 dead space is relatively greater, and the CO_2 dead space relatively smaller.

TABLE V.

Experiment No.	Rate of Running.	Mixture breathed.	Oxygen Requirement in litres.	Tidal Air in c.c.	Oxygen Dead Space in c.c.	CO_2 Dead Space in c.c.	Dead Space Ratio.
Resting in Air.			—	552	136	131	1.01
(Average of all Experiments.)							
1	168	Air	20.69	1950	—	—	—
2	184	Air	—	2150	350	299	1.17
3	200	Air	—	2000	339	306	1.11
4	220	Air	23.75	2140	309	285	1.085
5	200	26 % O_2	24.23	2010	202	242	0.84
6	220	26 % O_2	26.04	2060	185	272	0.68
7	200	16 % O_2	21.06	2340	464	377	1.23
8	220	16 % O_2	21.84	2260	550	444	1.24
9	200	5 % CO_2	21.44	2460	473	521	0.91

Average tidal air, O_2 dead space, CO_2 dead space, and dead space ratio in all experiments on Subject No. 4.

Subject No. 5. Student, aged 22. Height 184 cm. Weight 75 kg. Vital capacity 5,610 c.c. Heavily built. A good swimmer, but with no experience of and no natural aptitude for running.

Three sets of experiments were performed on this subject. The expired air during the first seven minutes of work in each experiment was collected into one large bag, while that of the last minute of work only was collected into a separate bag. The expired air during the first nine minutes of the post-exercise period was collected into six separate bags at increasing time intervals, and the rest of the expired air up to thirty minutes from the cessation of work was then collected into one large bag. The alveolar air was collected during the last minute of work only, and at intervals during the first nine minutes of the post-exercise period. His post-absorptive resting metabolism breathing air, in all seven experiments, is shown in Table VI, and the O_2 requirement, O_2 debt, and O_2 income in each experiment in Table VII.

Three experiments (Exps. 1, 2, and 3) were performed at increasing rates of running breathing air (Fig. 20); in Experiment 2 alveolar observations were incomplete. We have the impression that this subject over-breathed considerably during the first 6½ minutes of the post-exercise period in Experiment 1, as the respiratory quotient and the pulmonary ventilation seem much too high, and the percentage O_2 absorption and CO_2 excretion much too low, when the big difference in oxygen requirement between this experiment and Experiments 2 and 3 is taken into consideration. One experiment (Exp. 4) was performed running at 190 steps per minute breathing approximately 26 per cent. O_2 ; in Fig. 21 this experiment is set out graphically to the left of the corresponding experiment in which air is breathed. The two experiments differ slightly, and the subject did not notice any subjective difference when breathing the higher O_2 percentage. Two experi-

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ments were performed while breathing approximately 16 per cent. O₂, one running at 190 steps per minute (Exp. 5, Fig. 21) and one at 210 (Exp. 6, Fig. 22); in the figures referred to these experiments are set out graphically to the right of the corresponding experiment when breathing air. The subject noticed the difference in both these low O₂ experiments; after Experiment 7 he was very exhausted, and during this experiment was particularly conscious of a feeling of stiffness in the legs. In Fig. 23 the 'totals' for the work period in all these experiments, and in Fig. 24 the percentage of O₂ requirement as income, and the

TABLE VI.

Experiment No.	Pulmonary Ventilation. Litres per Minute.	Respiration Rate.	Tidal Air. c.c.	O ₂ absorbed. c.c. per Minute.	CO ₂ excreted. c.c. per Minute.	R. Q.	% O ₂ absorbed.	% CO ₂ excreted.	Alveolar O ₂ %.	Alveolar CO ₂ %.
1	7.90	18	439	244	218	0.89	3.58	3.20	6.02	5.42
2	9.64*	18	536	300*	286*	0.95	3.60	3.43	6.38	5.38
3	7.14	12.5	571	256	223	0.89	4.14	3.69	6.20	5.56
4	8.19	18	454	234	217	0.93	3.34	3.10	6.16	5.21
5	7.25	18	404	241	193	0.80	3.82	3.05	6.45	5.37
6	7.75	13.5	574	251	233	0.93	3.80	3.55	6.10	5.39
7	—	13.5	—	—	—	0.74	4.74	3.49	6.75	5.57
Aver.	7.65	16	496	245	218	0.86	3.86	3.36	6.29	5.41

The resting respiratory exchange (post-absorptive) in all experiments on Subject No. 5. Starred values have been neglected in the calculation of averages as being due to technical errors. Experiment No. 7 was not subsequently completed.

TABLE VII.

Experiment No.	Rate of Running. Steps per Minute.	Gas Mixture breathed.	O ₂ Income. Litres.	O ₂ Debt. Litres.	O ₂ Requirement. Litres.	% of Requirement as Income.	% of Requirement as Debt.
1	168	Air	15.47	2.34	17.81	86.9	13.1
2	190	Air	19.46	4.48	23.94	81.3	18.7
3	210	Air	19.16	5.35	24.51	78.2	21.8
4	190	25.81 % O ₂	19.64	4.79	24.43	80.4	19.6
5	190	15.57 % O ₂	17.22	4.41	21.63	79.6	20.4
6	210	15.54 % O ₂	18.68	4.77	23.45	79.7	20.3

Oxygen income, oxygen debt, and oxygen requirement in all experiments on Subject No. 5.

'total' respiratory quotient, ventilation, percentage O₂ absorption, and percentage CO₂ excretion during the first 6½ minutes of the recovery period for each of these experiments, are plotted against the O₂ requirement of that experiment. Alveolar observations were recorded only during the last minute of work in this subject, and the dead space ratios are therefore all that can be calculated. These were approximately the same at rest and during the last minute of work breathing all mixtures; this subject did not exhibit the phenomena as regards the dead space ratio found in Subject No. 4.

IV. Summary of Experimental Results.

In summarizing our experimental results we have proceeded on the following lines. The graphs of all experiments on each subject have been inspected, and the corresponding curves in successive experiments compared in respect to

(a) their form, (b) their slope, and (c) their level. But as an ergometer was not used, the actual amount of work any one of our subjects did, when running at the same number of steps per minute in successive experiments in which different gas mixtures were breathed, was not always quite the same; for this reason such experiments are not strictly comparable with each other. Reference to Tables IV and VII shows that the oxygen requirement of the same rate of running when 26 per cent. oxygen was breathed was usually greater, and the oxygen requirement of the same rate of running when 16 per cent. oxygen or 5 per cent. carbon dioxide was breathed was almost invariably less, than the oxygen requirement of the same rate of running when air was breathed. Clearly, our subjects did more work and ran more vigorously and in better style under high oxygen pressure, and did less work and ran in poorer style under low or in 5 per cent. carbon dioxide; this was also our impression at the actual time of the experiments. When comparing the graphs of such experiments, therefore, it must be remembered that the subject when breathing 26 per cent. oxygen was usually working harder, and when breathing 16 per cent. oxygen or 5 per cent. carbon dioxide less hard, than in the corresponding experiment at the same rate of running when he was breathing air. To assist in making these comparisons, we have therefore plotted, on the same graph for each subject, the 'totals' (see p. 395) calculated for the whole of, or for the same part of all experiments against the average oxygen consumption per minute (Subjects 1, 2, and 3), or against the oxygen requirement of the work done (Subjects 4 and 5). The oxygen requirement of exercise is, of course, the true measure of the energy expended, but as in Subjects 1, 2, and 3 the oxygen debts were not determined, the 'totals' have been plotted against average oxygen consumption per minute instead, as an approximate index of the amount of energy expended in each experiment. In looking at the figures (Figs. 6, 8, and 13) summarizing all the experiments on each of these three subjects, it must be remembered that, as with increasing rate of work the magnitude of the oxygen debt increases relative to the amount of oxygen taken in during work, the curves rise more steeply than would have been the case if it had been possible to plot the calculated 'totals' against oxygen requirement. For the reasons given above, in these diagrams for Subjects 3, 4, and 5 (Figs. 13, 18, 19, 23, and 24) the points for the 26 per cent. oxygen experiments usually fall to the right, and the points for the 16 per cent. oxygen and 5 per cent. carbon dioxide experiments to the left, of the points for the corresponding air experiments at the same rate of running. When these graphs are examined, the curves must not be imagined extended farther to the right. At the highest rate of running the subjects were certainly completely exhausted when breathing 16 per cent. oxygen, and very nearly so when breathing air. Points farther to the right could not have been obtained because the subjects could not have accomplished greater rates of work; but breathing 26 per cent. oxygen they were capable of doing so.

Before actually summarizing our results something must be said as to the interpretation we put on our alveolar air observations on Subjects Nos. 4 and 5. All that we claim is, that the true average composition of the alveolar air during

exercise must be somewhere between the composition of the alveolar air collected by our method, and that of the expired air collected over the same time interval. In the graphs for experiments on Subject No. 4 it will be seen that the curve showing the percentage of CO_2 in the alveolar air runs parallel with the curve showing the percentage of CO_2 in the expired air, and that the curve showing the percentage of O_2 in the alveolar air corresponds with the curve showing the percentage of O_2 taken out of the inspired air. The percentage of CO_2 and the percentage of O_2 in the alveolar air rise and fall approximately parallel with the percentage of CO_2 and the percentage of O_2 in the expired air after the first few minutes of a steady rate of work. In all experiments, therefore, changes in the expired air are taken to mean similar changes in the composition of the alveolar air.

The number of subjects investigated has been small, but on the other hand many experiments have been performed on each one, and certainly as much was demanded of most of them as each could stand before he became hopelessly 'stale'; moreover, each experiment was planned on a large scale, and was an undertaking of considerable magnitude. On the whole, the experimental results obtained seem fairly uniform considering the nature of this kind of experimental work, the extent to which psychological factors influence the volume of ventilation, and the possible variations in the physical and mental fitness of our subjects from day to day. Major irregularities in the curves are frequently to be attributed to the subject not maintaining his rate of work very constant, or to slacking off as subjective distress supervened, rather than to technical errors.

Our experimental results are not altogether consistent, but what we consider to be a fair summary, bearing these various considerations in mind, will now be given; no useful purpose would be served by discussing each experiment or subject separately. Perhaps the most striking inconsistency is the very slight effect of breathing 26 per cent. oxygen on the respiratory exchange in Subject No. 5 when running at 200 steps per minute; unfortunately it was not possible to investigate this subject breathing a high oxygen mixture at a greater rate of work. This subject was an indifferent runner; the effect of breathing 26 per cent. oxygen was much greater on our two good runners, Subjects 3 and 4.

*The Respiratory Exchange at Increasing Rates of Work breathing Air
at Ordinary Barometric Pressure.*

When a man works at a constant rate for the same number of minutes (5-10) in each experiment, but at increasing rate of work in successive experiments (with consequent increase in the oxygen requirement of the work done), the respiratory exchange behaves in the following way.

A. *In all experiments the following changes occur during the course of the work period (see Figs. 5, 7, 9, and 14):*

1. The O_2 intake and CO_2 output per minute rise rapidly to an approximate maximum in about the third minute; the O_2 maximum is sustained, but the CO_2 output then falls. The respiratory quotient rises to a maximum in the third minute and then falls, but does not return to its resting value.

2. The O_2 percentage in the expired air is minimal, and the percentage O_2

absorption from the inspired air maximal, during the first minute of work. The percentage in the expired air then rises rapidly, and the percentage O_2 absorption falls correspondingly until the third minute or so, when, with the reduction in the ratio of the volume of the dead space to the volume of tidal air with increased depth of breathing, the percentage of O_2 in the expired air has approximated much more closely to the percentage of O_2 in the alveolar air than at rest. Thereafter, at the lower rates of work, the percentage O_2 absorption, the percentage of O_2 in the alveolar air, and the percentage of O_2 in the expired air all remain constant. At higher rates of work, the alveolar and expired air O_2 percentages rise progressively and are maximal at the end of the work period, while the percentage O_2 absorption falls progressively and is minimal at the end of the work period.

3. With the sudden fall in the ratio of the volume of the dead space to the volume of the tidal air with increased depth of breathing, the percentage CO_2 excretion rises to a maximum in the second or third minute of work, and now approximates much more closely to the percentage CO_2 in the alveolar air than at rest. At the lower rates of work these percentages then remain constant, but at the higher rates of work they fall off progressively, and both are minimal at the end of the work period.

4. The pulmonary ventilation and the respiration rate rise rapidly at first until the maximum O_2 intake and CO_2 output have been attained. At the lower levels of work they then remain constant, but at higher rates of work they both rise progressively until the end of the work period.

B. *With increasing rate of work, comparing experiments where the oxygen requirement is greater with experiments where the oxygen requirement is less.* (See Figs. 5-8, 9, 13, 14, 18, 20, 23.)

1. All curves rise or fall more steeply.

2. The O_2 intake per minute rises until a rate of work is sooner or later attained at which further increase has no effect on the O_2 intake per minute.

3. The CO_2 output per minute rises progressively, but no maximum comparable to that described for the O_2 intake is attained.

4. The peak of the respiratory quotient curve is higher, and the total respiratory quotient calculated for the whole experiment numerically greater; at low rates of work below, but at high rates of work well above, unity.

5. The curve showing the percentage O_2 absorption is lower, and the percentage O_2 absorption calculated for the whole experiment is less.

6. The curve showing the percentage CO_2 excretion is lower, and the percentage CO_2 excretion calculated for a whole experiment is less.

7. The average alveolar O_2 and expired air O_2 percentages (excluding the first two minutes of each experiment) are higher, and the former usually well above its resting value.

8. The average alveolar CO_2 and expired air CO_2 percentages (excluding the first two minutes of each experiment) are lower, and the former usually well below its resting value.

9. The pulmonary ventilation is more than proportionately increased and the respiration rate quicker.

C. *During the early part of the recovery period following the abrupt cessation of running in all experiments.* (See Fig. 20.)

1. The O_2 intake per minute falls rapidly towards its resting value, while the output of CO_2 per minute falls less quickly. The respiratory quotient jumps up to a high maximum, and then falls quickly to its resting value.

2. The O_2 percentages in the alveolar and expired airs rise quickly to a maximum, and then fall rapidly towards their resting values. With the increase in the ratio of the volume of the dead space to the volume of the tidal air, as the depth of breathing decreases, these curves move apart. The percentage O_2 absorption falls off to a corresponding minimum, and then rises towards its resting value.

3. The alveolar CO_2 percentage falls rapidly to below its resting value, and the percentage CO_2 excretion falls off correspondingly. With the relative alterations in volume of dead space to tidal air, these curves move apart.

4. The pulmonary ventilation per minute, and respiration rate, fall off progressively, quickly at first, then more slowly.

D. *With increasing rate of work, comparing the early recovery period in experiments with greater oxygen requirement with the early recovery period of experiments with less oxygen requirement.* (See Figs. 19 and 24.)

1. The respiratory quotient calculated for the period is greater.

2. The percentage O_2 absorption for the whole period is less.

3. The percentage CO_2 excretion for the whole period is less.

4. The total pulmonary ventilation is greater.

E. *Oxygen requirement: income and debt.* (See Figs. 19 and 24 and Tables IV and VII.)

With increasing rate of work (increasing oxygen requirement) the percentage of requirement met out of income falls, and the percentage met out of debt rises.

The Respiratory Exchange at the same Rate of Work breathing Air, 26 per cent. and 16 per cent. Oxygen. (See Figs. 10, 11, 13, 15, 16, 18, 19, and 21-4.)

When a man works at the same constant rate for the same period of time, so that the oxygen requirement of the work done in three successive experiments, in which 26 per cent. oxygen, air (21 per cent. O_2), and 16 per cent. oxygen are breathed respectively, is the same, the respiratory exchange differs in the three experiments. These differences are most clearly shown by setting them out in a tabular form as under, where plus and minus signs indicate the relative values of the 'totals' calculated for each experiment.

	26 % O_2 .	Air, O_2 21 %.	16 % O_2 .
A. <i>Changes during work period:</i>			
1. Rate of rise and fall of curves	-	+	++
2. Respiratory quotient	-	+	++
3. Percentage O_2 absorption	++	+	-
4. Percentage CO_2 excretion	++	+	-
5. Alveolar and expired air O_2 % (relative)	-	+	++
6. Alveolar CO_2 percentage	++	+	-
7. Pulmonary ventilation	-	+	++

	26 % O ₂ .	Air, O ₂ 21 %.	16 % O ₂ .
<i>B. Post-exercise period (up to half an hour):</i>			
1. Respiratory quotient	-	+	++
2. Percentage O ₂ absorption	++	+	-
3. Percentage CO ₂ excretion	++	+	-
4. Pulmonary ventilation	-	+	++
<i>C. Oxygen requirement: income and debt:</i>			
1. Percentage of requirement as income	++	+	-
2. Percentage of requirement as debt	-	+	++

The Respiratory Exchange at the same Rate of Work breathing Air and 5 per cent. Carbon Dioxide. (See Figs. 12, 13, 17-19.)

Only two experiments, one on each of two subjects, were performed under these conditions; our conclusions are therefore less general and less definite. The forms of the curves are approximately the same as in the corresponding experiments during which air was breathed.

For work of the same oxygen requirement when 5 per cent. carbon dioxide is breathed as opposed to air:

1. The peak of the respiratory quotient curve is lower, and the respiratory quotient calculated for the whole experiment is less.
2. The percentage O₂ absorption curve is lower, and the percentage O₂ absorption calculated for the whole experiment is less.
3. The percentage CO₂ excretion curve is lower, and the percentage CO₂ excretion calculated for the whole experiment is less.
4. The average alveolar and expired air O₂ percentages are much greater.
5. The average alveolar CO₂ percentage (relative to the percentage of CO₂ in the inspired air) is much less.
6. The pulmonary ventilation is greater, but the respiration rate about the same, and the depth of breathing therefore much greater.

As regards the relationships which may exist between the relative magnitude of the O₂ income and O₂ debt during work of a given O₂ requirement, when 5 per cent. CO₂ is breathed instead of air, no very definite statement can be made. Our earliest experiments, in conjunction with H. N. Bradbrooke, and briefly communicated to the Physiological Society (13), were an attempt to determine whether breathing 5 per cent. CO₂ reduced the maximum O₂ intake of which a man is capable; this it seemed to do to the extent of about 10 per cent. Breathing high percentages of CO₂ does considerably limit the amount of work a man can do (*vide* Hill and Flack (41)), and watching our subjects run certainly suggested that the reduction in the amount of work of which they were capable was greater than could be accounted for by the decrease in the O₂ intake which we observed, suggesting that the extent to which they were able to incur debt was also reduced. Experiment No. 9 on Subject No. 5, however, seems to show that after moderately severe work breathing CO₂, the decreased O₂ intake during work results in a greater O₂ debt being left over at the end. If this is so, then the effect of breathing CO₂ on the income-debt relationships of muscular work is

similar to that of reducing the O_2 pressure in the inspired air (*vide infra*). But these CO_2 experiments were not satisfactory in consequence of the specific effect of high percentages of CO_2 on the subjects. They became deadly white, ran badly, and even became slightly ataxic. Questioned afterwards, they complained of headache, nausea, and diminished consciousness of things in general, so that the passage of time seemed rapid; that they had difficulty in following the metronome, or that the ticking of the metronome seemed far away: they did not make any particular complaint of respiratory distress. It seems that the effect of CO_2 on the limitation of voluntary effort is largely due to this semi-narcotic action, and only to a minor extent to any influence on the chemical changes responsible for muscular movement. As, therefore, they are likely to throw little light on the mechanism of the limitation of effort when oxygen-nitrogen mixtures are breathed, we have thought it useless to pursue such experiments any farther.

Many of the alterations in the respiratory exchange during exercise, which have just been described, confirm the results of other workers. No attempt will be made to review the literature, but recent papers on muscular exercise, which have a particular bearing on the aspect of the problem under consideration, and especially those dealing with the respiratory exchange during exercise under high and low barometric pressure, will now be referred to.

Ordinary barometric pressure. Campbell, Douglas, and Hobson (11) have shown that the respiratory quotient rises during work (often to well above unity), and continues to do so for a minute or two after the cessation of work, and that with increasing rates of work this rise becomes progressively more pronounced, observations confirmed by Hill, Long, and Lupton (36) and by Schneider and Clarke (80). Henderson and Haggard (31), however, who investigated the respiratory exchange in trained oarsmen, failed to find rises in the respiratory quotient during rowing comparable to those described by Hill. Hill, Long, and Lupton have also described the rise in the oxygen intake per minute to a maximum of which the individual is capable (39), and the progressive increase in the magnitude of the oxygen debt as the rate of work is increased beyond the limits of the steady state (38). Douglas and Haldane (17) found that the carbon dioxide tension in the alveolar air was increased immediately after the cessation of severe exercise of brief duration, but diminished progressively for several minutes after exercise stopped, and remained lower than normal for half an hour or more. Corresponding results have been obtained by Barr and Himwich (7, 8, 9), who actually determined the carbon dioxide tension in the arterial blood during and after exercise (see p. 411). They also found that during more prolonged exercise the carbon dioxide tension of the arterial blood fell to below its resting value during exercise itself. Briggs (10) has paid particular attention to the percentage of carbon dioxide in the expired air during exercise, and investigated the respiratory exchange during increased rates of measured work up to 12,000 foot-pounds per minute on a bicycle ergometer. At each rate of work one determination only of the respiratory exchange was

made, and this two minutes after its commencement. The percentage of carbon dioxide in the expired air was found to rise with increased rate of work, until an 'overload' was reached (6,000 foot-pounds per minute or thereabouts in most individuals), after which the percentage of carbon dioxide fell off progressively with further increase in the rate of work. Briggs came to the conclusion that the ability to do work with little pulmonary ventilation, and therefore excrete carbon dioxide in a high percentage, was a measure of the physical fitness of the individual.

High oxygen pressures. Leonard Hill and Flack (42) described the beneficial effect of previous inhalation of oxygen on muscular exertion, and showed that it enables athletes to stand a higher percentage of carbon dioxide in their alveoli than would otherwise be the case, an observation confirmed by Cook and Pembrey (15). Briggs (10) found that breathing 50-60 per cent. oxygen enabled a man to do the same amount of measured external work on an ergometer with less pulmonary ventilation, and therefore to excrete carbon dioxide at a higher percentage in the expired air; this beneficial effect of breathing oxygen was apparent at all rates of work in the unfit subject, but only observed with overloads in well-trained individuals. He also found that at the same rate of work the oxygen consumption was less when 50 per cent. oxygen was breathed than when air was breathed, and concluded that muscular work was performed more efficiently under increased oxygen pressure. But as the percentage of oxygen in the inspired air was very high, as ten minutes only were allowed for equilibration under the new oxygen pressure, and as the determination of the respiratory exchange was made only two minutes after work commenced, his results are possibly open to criticism. Hill, Long, and Lupton have also investigated the effect of breathing high oxygen mixtures (round about 50 per cent.) on muscular exercise. Raising the oxygen pressure in the inspired air considerably increased both the maximum oxygen intake per minute which a man could effect (39), and also the size of the maximum oxygen debt that he could incur, but during a given severe effort (as opposed to running 'all out') increased oxygen pressure, by causing a greater oxygen intake per minute during work, led to a smaller oxygen debt being left over at the end (37, p. 125). Raising the oxygen pressure in the inspired air invariably lowered the respiratory quotient both during and after cessation of exercise (37, 39), but they did not demonstrate any consistent reduction in the volume of ventilation as in Briggs's experiments and in our own.

Low oxygen pressures. Schneider and Clarke (79, 80) have shown that, at the same rate of external work, the respiratory quotient and pulmonary ventilation are greater, and the percentage of oxygen taken out of the inspired air less, under reduced barometric pressure, as we also have found. The experiments of Hill, Long, and Lupton, as presented, do not demonstrate these relationships. Few, however, of their experiments are directly comparable; either the rate, or the duration, or the nature of the work in successive experiments, was varied. Moreover, though the recovery process was usually followed in detail, a single determination was usually all that was made of the respiratory exchange itself. We have the impression, after reading their papers very carefully, that the

amount of work done by their subjects under low oxygen pressure was definitely less than at the same rate of running under normal conditions, as in our experiments. If the work had been standardized, or the results of different experiments plotted against oxygen requirement, similar relationships between respiratory quotient, pulmonary ventilation, and oxygen pressure would probably have been established as those described by Schneider and Clarke, which our experiments confirm. Hill, Long, and Lupton also investigated the effect of reduction in the oxygen percentage in the inspired air (as far down as 11 per cent.), and found it to reduce the maximum oxygen intake of which a man is capable. No definite statement is, however, made as to whether it also reduces the size of the maximum oxygen debt which a man can incur, but their experiments (37, p. 121, Table V, Exps. 5, 6, 7, and Fig. 4) suggest that this is so. This point has since been taken up by Schneider and Clarke (79), who have determined the respiratory exchange during the last two minutes of five minutes' work, ranging from 2,000 to 6,000 foot-pounds per minute on a bicycle ergometer under barometric pressure, progressively reduced as far down as 290 mm. Hg (25,000 ft.), allowing ten minutes for equilibration in each experiment under a new pressure. They found that reduction in barometric pressure decreased the rate of oxidation in the body, and they describe a linear relationship between the degree of reduction of barometric pressure and the extent to which oxygen intake per minute at constant rate of work was reduced. They were therefore led to anticipate that the reduction in the oxygen intake during the same amount of work under reduced barometric pressure would be compensated for by a corresponding increase in the magnitude of the oxygen debt, the oxygen requirement of the same amount of external work remaining the same. Schneider and Clarke therefore determined the respiratory exchange during each minute of eight minutes' work (4,000 foot-pounds per minute), and followed the recovery period for twenty-two minutes, both under normal conditions and under reduced barometric pressure. In this paper (79), and in a preceding one (81), they produce evidence which leads them to suppose that at a barometric pressure below 410 mm. Hg (10,000 ft.) the resting oxygen consumption of the body is reduced. In their calculations they take the resting oxygen consumption under reduced barometric pressure as their base-line, which of course makes the oxygen income greater, and the oxygen debt greater still, than if the resting oxygen consumption under ordinary conditions had been employed. As their results raise the question of the validity of the principle on which the calculation of the oxygen debt at the end of exercise is based, we have set out their results in tabular form on p. 408, and also, in each of their experiments, calculated the percentage distribution of the oxygen requirement of the work done between income and debt.

From these figures it appears that the reduced oxygen intake during work was not compensated for by a corresponding increase in the magnitude of the oxygen debt. This may mean that the oxygen requirement of a given amount of external work is less under low barometric pressure, i. e. that the efficiency of the body as a whole is increased; but Briggs's experiments already cited suggest

the opposite of this. On the other hand, it is possible that the principle on which oxygen debts are calculated is invalid, i. e. the energy requirements of the body at rest, and the excess energy requirements of muscular work, are not arithmetically summed. Perhaps the resting metabolic rate is in excess of the absolute needs of the body, and so can be drawn upon both during resting and working conditions under low barometric pressure, and, if so, possibly during work under ordinary circumstances as well. Again, under resting conditions some energy expenditure is required to maintain the body temperature, but during work the body temperature is wholly maintained and probably unduly raised by the unavoidable energy cost of external work. In both cases calculation of the oxygen requirement of the work done by subtracting the resting oxygen

Baro- meter.	Actual O ₂ Intake during Work.	Actual O ₂ Intake during Recovery.	Oxygen Income.	Antici- pated O ₂ Debt.	Actual O ₂ Debt.	Oxygen Require- ment.	% O ₂ Require- ment as Income.	% O ₂ Require- ment as Debt.
<i>Subject R. W. C.</i>								
764	11023	6149	9159	—	1023	10182	90	10
447	10088	6141	8336	1847	1323	9659	86	14
415	9024	6113	7576	2606	2131	9707	78	22
<i>Subject E. W. G.</i>								
756	10599	7346	8295	—	1010	9305	89	11
457	8305	7092	6353	2952	1726	8079	79	21
415	8501	6827	6301	3004	769	7070	89	11
<i>Subject H. H.</i>								
760	11957	6585	9901	—	1445	11346	87	13
410	9624	6543	7384	3962	843	8227	90	10

consumption from the total oxygen intake during work and recovery would give erroneous results. Although not convinced that the principle on which oxygen debts are calculated is necessarily valid, we are inclined to attribute the remarkable results obtained by Schneider and Clarke to the fact that they only followed the recovery period for twenty-two minutes—a dangerously short, and probably insufficient, period of time on which to base a calculation of the oxygen debt, in view of the very low barometric pressures with which they were working. If this is so, then their debts as determined are all too small, particularly at the lowest oxygen pressure. But even as their results stand, they give partial support to our finding that with reduced oxygen pressure the percentage of oxygen requirement incurred as debt is increased.

V. Discussion of Experimental Results.

The alteration in the respiratory exchange during exercise with increasing rates of work. During muscular effort the respiratory exchange becomes altered in a way which has now been described. With increasing rate of work, the volume of pulmonary ventilation required to effect the intake of unit quantity of oxygen and excretion of unit quantity of carbon dioxide rises progressively. With increasing rate of work, less and less oxygen is taken out of the same

volume of inspired air, and less and less carbon dioxide added to it; the alveolar O_2 tension rises and the alveolar CO_2 tension falls. (See Figs. 6, 8, 13, and 18.) Similar alterations in the respiratory exchange are brought about *under resting conditions*, by high altitudes, or low oxygen pressure experimentally produced, and also by pathological or experimental acidosis.

The regulation of breathing, even under resting conditions, is not completely understood (for literature on the subject the reader is referred to reviews by Means (59) and Yandell Henderson (30)), but from its physico-chemical aspect there seem to be three outstanding factors which govern the behaviour of the respiratory centre.

1. The cH (hydrogen-ion concentration) of the blood plasma is determined by the ratio of the amount of dissolved CO_2 (H_2CO_3) to the amount of mono-valent bicarbonate ($BHCO_3$) in accordance with the equation:

$$cH = \frac{H_2CO_3}{BHCO_3} \times \text{constant (Hasselbalch)}.$$

2. The respiratory centre is stimulated by rise of cH of the arterial blood plasma (J. S. Haldane).

3. The extent to which the respiratory centre responds to rise of cH is determined in such a way that:

$$\frac{O_2 \text{ pressure in alveolar air}}{\text{plasma bicarbonate}} = \text{constant (Yandell Henderson)}.$$

High altitudes bring about these respiratory changes in the following way. The reduced oxygen pressure lowers the O_2 pressure/ $BHCO_3$ ratio, and makes the respiratory centre more sensitive to the same rise in cH of the arterial blood plasma. Over-breathing relative to the requirement of the body for carbon dioxide elimination under resting conditions is therefore produced, and the tension of CO_2 in the alveolar air and arterial blood falls, an excess of CO_2 being washed out of the blood with rise of respiratory quotient; the plasma $H_2CO_3/BHCO_3$ ratio and the cH of the plasma fall. But the kidney slowly responds by excreting bicarbonate, with consequent lowering of the CO_2 dissociation curve and CO_2 -carrying power of the blood, until the latter is so reduced as to compensate for the increased breathing, when elimination of CO_2 by the lungs again corresponds with the metabolic demand, and the respiratory quotient returns to normal. A new equilibrium has now been established. The plasma H_2CO_3 , the plasma $BHCO_3$, and the alveolar CO_2 tension are all low, but the $H_2CO_3/BHCO_3$ ratio of the plasma, the cH of the plasma, and the O_2 pressure/ $BHCO_3$ ratio have returned to normal. The respiratory centre is now responding as before to rise in the cH of the plasma, but the increased ventilation is kept up by the decreased buffering power of the blood, as the same addition of CO_2 to the same volume of blood now causes a greater rise in cH than before. In consequence of this increased ventilation less O_2 is taken out of the inspired air, and the alveolar O_2 pressure rises. More pulmonary ventilation is now being required to effect the intake of unit quantity of O_2 and the excretion of unit quantity of CO_2 .

But qualitatively identical final alterations in the respiratory exchange will

be brought about, by a different method however, when acid other than carbonic is added to the blood. The addition of strong acid, by combining with base, lowers the buffering and CO_2 -combining power of blood, and also lowers the BHCO_3 of the plasma. The addition of the same quantity of CO_2 to unit volume of blood now causes a greater rise of cH than before. The respiratory centre is therefore stimulated, and the increased breathing washes CO_2 out of the blood with rise of respiratory quotient, until the CO_2 tension in the arterial blood and alveolar air is so reduced that the increased ventilation again corresponds to the metabolic demand for the elimination of CO_2 , and the respiratory quotient returns to normal. A new equilibration has now been established. The plasma H_2CO_3 , the plasma BHCO_3 , and the arterial and alveolar CO_2 tensions are all lower, but the plasma $\text{H}_2\text{CO}_3/\text{BHCO}_3$ ratio and the cH of the plasma have returned to normal. The increased ventilation is now kept up by decreased buffering power and corresponds with the decreased CO_2 -carrying power of the blood; less O_2 is taken out of the inspired air and the alveolar O_2 tension rises. More pulmonary ventilation is now being required to effect the intake of unit quantity of O_2 and the excretion of unit quantity of CO_2 . [This comparatively simple statement of acidosis has, however, been recently called in question by Yandell Henderson (30), who emphasizes the difference between the addition of acid to the blood *in vitro*, and the addition of acid to the blood in the body with all the regulating mechanisms of the organism intact. He points out that it is not infrequent to see a patient with diabetic acidosis, with a raised cH of the blood plasma and a lowered CO_2 -combining power of the blood, who could, so to speak, if he liked, by breathing rather more, restore the hydrogen-ion concentration of his blood to normal. He therefore claims that the immediate cause of acidosis must be *relative* depression of breathing, due to relative reduction in plasma bicarbonate to the O_2 pressure in the alveolar air.]

The alterations in the respiratory exchange brought about by increasing rate of work may therefore be due either to progressive anoxaemia, as in acclimatization to high altitudes (or to over-breathing due to other causes—rise of body temperature, for instance), or to progressive acid production as in pathological acidosis. The Hill-Meyerhof conception of muscular contraction (with the production of lactic acid 'as part of the machine') suggests the latter explanation. But a definite answer to the question can be given by chemical examination of the blood. If the alterations in the respiratory exchange with exercise are due to primary over-breathing, the CO_2 -combining power of the blood will be reduced and its cH shifted in the alkaline direction; but if they are due to acidosis, while the CO_2 -combining power will again be reduced, the cH of the blood will be shifted to the acid side.

Christiansen, Douglas, and Haldane (12) found a diminution of 40 per cent. in the CO_2 -combining power of the whole venous blood of one subject after exercise, Harrop (27) a reduction in the CO_2 content of both the arterial and venous blood in one subject, and Lindhard (52) a lowering of the CO_2 -combining capacity in two subjects after exercise. Barcroft (3) found changes in the oxygen dissociation curve of the finger blood after a climb up Carlingford Mountain,

indicating a rise of hydrogen-ion concentration. Parsons and Barcroft (61) have directly demonstrated rise of hydrogen-ion concentration of the finger blood during moderate work on a bicycle ergometer (hydrogen electrode). Barr, Himwich, and Green (9) and Barr and Himwich (7, 8) have, however, made the most extensive investigation of the chemical changes in the blood during and after exercise. The CO_2 absorption curve (CO_2 combining power) and CO_2 tension in both the arterial and venous bloods, collected three minutes after the cessation of 3,500 kilogrammetres of work in $3\frac{1}{2}$ minutes, were determined, and the pH of both the arterial and venous bloods calculated from Hasselbalch's equation. They found a fall from the resting value in the CO_2 absorption curve of the arterial blood (maximum fall at 40 mm. CO_2 tension, 42 per cent. of the resting value), a fall in the arterial CO_2 tension (maximum fall 13.5 mm. Hg), and a fall in the arterial pH (maximum fall 0.25) in all the subjects investigated. With light work these changes in the acid-base balance of the blood were scarcely detectable, but with heavy work the degree of change, both in the reaction and CO_2 combining power, increased rapidly with each small increment in the amount of work done. Barr and Himwich also found that the slope of the CO_2 absorption curve of blood is flatter after exercise; in consequence of this, the efficiency of blood as a carrier of CO_2 must be progressively reduced during exercise, as in the change between any two physiological CO_2 tensions a given volume of blood takes up less CO_2 from the tissues and eliminates less CO_2 in the lungs. In 1920 Haggard and Henderson (24) suggested that acapnia occurs in exercise, i.e. primary over-ventilation by the lungs with resultant alkalosis; this would be followed by a compensatory reduction in the blood bicarbonate which might be in part accomplished, as Macleod (57) has shown, by the production of lactic acid. Barr and Himwich (8) therefore investigated the chemical changes in the arterial blood *during* muscular exercise, and found that during work of 3.5 minutes' duration the CO_2 capacity of the arterial blood began to diminish during the second minute, and did not reach its minimum until three minutes or so after work stopped; the arterial CO_2 tension was increased during the first two minutes of work, but started to fall and reached its minimum some minutes after work stopped. During work of longer duration (7.5 minutes) the maximum changes in the CO_2 capacity, CO_2 tension, and blood reaction occurred during exercise itself. Their conclusion is worth quoting: 'The response to exercise is not an acapnia phenomenon. The CO_2 capacity (bicarbonate) of the blood was diminished at a time (second minute of exercise) when the CO_2 tension was increased, and when respiration was inadequate to remove all of the CO_2 which was produced. At no time was there an alkalosis. Even during the second minute of work there was a marked diminution in alkalinity, which was progressive as the exercise continued, and from one to three minutes after the exercise ceased.' Additional evidence of progressive lactic acid acidosis during muscular exercise is furnished by Hill, Long, and Lupton (36), who found that with increasing rate of work the percentage of lactate in the blood rises considerably, while the oxygen debt incurred, which depends upon the total amount of

lactate accumulated, increases. They point out, however, that the rise of the respiratory quotient during work is too small to be explained by neutralization of the lactic acid accumulated (calculated from the magnitude of the O_2 debt) by bicarbonate with evolution of CO_2 , and that its neutralization must be almost entirely effected by the sodium-protein buffers of muscle with the liberation of an equivalent amount of acid protein (unionized protein), and consequent rise of cH. The respiratory centre is stimulated, and an excess of CO_2 is eliminated with rise of respiratory quotient, so that the cH tends to revert to normal, but it can only return actually to normal when the excess of CO_2 eliminated is chemically equivalent to the amount of lactic acid set free; during severe exercise this is far from being the case. 'Clearly we must admit', they write, 'that the hydrogen-ion concentration of the blood and tissues can rise, and rise considerably, during muscular exercise.' When exercise ceases, this rise of cH continues to stimulate the respiratory centre and drive off CO_2 , but at the same time the O_2 intake is falling rapidly, partly on account of diminished blood-flow, and partly on account of diminished rate of utilization of oxygen as recovery proceeds; on the cessation of exercise, therefore, the respiratory quotient jumps up to a high maximum before returning slowly to its resting value.

Whether the reduction in the CO_2 -carrying power of the blood during exercise can be entirely accounted for by the neutralization of base by lactic acid is at present uncertain. Barr, Himwich, and Green (9) estimated the lactate in the blood after exercise, and found that a rise in its lactate content was associated with a fall in its CO_2 -carrying power, but they failed to demonstrate a quantitative relationship between the two. Haggard and Henderson (25) and Henderson (30) do not think that the reduction in the CO_2 -combining power of the blood during exercise is entirely due to the accumulation of lactate. They argue that as most of the alkali for the neutralization of lactic acid must come from the haemoglobin alkali reserve of the corpuscles, reduction in the CO_2 capacity of the blood as ordinarily measured is not a valid index of the total reduction of the alkali reserve of the blood; that a reduction of, say, 10 per cent. of the CO_2 -combining power of the blood cannot therefore be regarded as due to lactic acid unless many times as much lactic acid on a molecule for molecule basis can be found in a neutralized form in the blood and urine. Yandell Henderson (30) supposes that during exercise, for some reason unknown, alkali is withdrawn from the blood into the tissues with a consequent rise of cH of the plasma. The O_2 pressure/ $BHCO_3$ ratio would then be raised with relative depression of breathing; that the breathing is actually depressed relative to the cH of the arterial blood during exercise has been shown by Barr and Himwich (6), who found that the cH of the arterial blood might be actually rising while the pulmonary ventilation was falling.

But the fact remains: during exercise the CO_2 -carrying power of the blood is reduced, with rise in the cH and lactate content of the arterial blood. During work a progressive acidosis develops, whether it be due in part to abstraction of alkali from the blood, as Yandell Henderson supposes, or, as is usually thought, entirely due to addition of lactic acid to it. Though primary over-breathing due

to anoxaemia, rise of body temperature, or other causes, may play a part in their production, the alterations in the respiratory exchange with increasing rates of work must be chiefly due to progressive acidosis. This mechanism of their production is therefore clear; the rise of cH of the arterial blood stimulates the respiratory centre and an excess of CO_2 is eliminated with rise of respiratory quotient; the decreased CO_2 -carrying power of the blood demands more pulmonary ventilation to eliminate unit quantity, and the tension of CO_2 in the alveolar air and the percentage of CO_2 in the expired air falls; less O_2 is taken out of the inspired air, and the alveolar O_2 tension and percentage of O_2 in the expired air rise. With increasing rate of work, therefore, more and more ventilation becomes necessary to eliminate unit quantity of CO_2 , as the CO_2 -carrying power of the blood is progressively reduced.

The alterations in the respiratory exchange during exercise with increase and decrease of the oxygen pressure in the inspired air. The alterations in the respiratory exchange at the same rate of work, when 26 per cent. oxygen and when 16 per cent. oxygen are breathed, have been described, and are qualitatively identical with alterations in the respiratory exchange with increasing rate of work, when air (21 per cent. oxygen) is breathed. During work of the same duration and oxygen requirement, when 26 per cent. oxygen is breathed instead of air, the amount of pulmonary ventilation required to effect the intake of unit quantity of oxygen and the excretion of unit quantity of carbon dioxide is less. More O_2 is taken out of the inspired air and more CO_2 is added to it; the alveolar O_2 tension approximates less closely to the O_2 pressure in the inspired air, while the alveolar CO_2 tension rises. Conversely, when 16 per cent. oxygen is breathed instead of air, more pulmonary ventilation is required to effect the intake of unit quantity of oxygen and the excretion of unit quantity of carbon dioxide; less O_2 is taken out of the inspired air and less CO_2 added to it; the alveolar O_2 tension approximates more closely to the pressure of O_2 in the inspired air and the alveolar CO_2 tension falls. The effect of increasing or decreasing the oxygen pressure in the inspired air on the alterations in the respiratory exchange with increasing rate of work is therefore one of degree only. Thus the respiratory 'picture' of running at 200 steps per minute breathing 16 per cent. oxygen may be practically identical with that of running at 220 steps per minute breathing air, while the respiratory 'picture' of running 220 steps per minute breathing oxygen may be nearly identical with that of running at 200 steps per minute breathing air. (See Figs. 10, 11, 13, 15, 16, and 18.)

The same alteration in the respiratory exchange can therefore be effected either by increasing the rate of work and keeping the composition of the air breathed constant, or by decreasing the oxygen pressure in the inspired air and keeping the rate of work constant. Similarly, identical alterations in the respiratory exchange can be brought about either by decreasing the rate of work and keeping the composition of the air breathed the same, or by keeping the rate of work the same and increasing the oxygen percentage in the air breathed. This suggests that increasing the rate of work and lowering the oxygen pressure, and

decreasing the rate of work and raising the oxygen pressure, act by virtue of the same mechanisms—increased and decreased lactic acid accumulation respectively. Our conclusion is that during work of the same duration and oxygen requirement the degree of acidosis is greater when 16 per cent. oxygen is breathed, and less when 26 per cent. oxygen is breathed, than when air is breathed.

We are unaware of any work comparable with that of Barr and Himwich (on the blood changes during and after exercise when air is breathed), done on the blood changes with exercise breathing oxygen mixtures other than air, such as would definitely substantiate this conclusion. But the results obtained by Barcroft (4, p. 95) and his associates, using the Dale-Evans method on his recent Andes expedition, bear out the results obtained on his previous Monte Rosa expedition, namely, that a smaller amount of work produces the same rise in cH at high altitudes than at sea-level, observations confirmed by measurements by Parsons (61) (using the hydrogen electrode) of the cH of the blood after exercise under reduced barometric pressure in a respiration chamber. We can find no observation on the CO_2 -combining power or cH of the blood during work under increased barometric pressure, but there is other evidence which strongly supports the above conclusion. In the first place, during work of the same duration and oxygen requirement, the oxygen intake during work is greater, and the percentage of the total oxygen requirement of the work done incurred as debt is less, when 26 per cent. oxygen is breathed than when air is breathed; the oxygen debt is smaller, which means that the accumulation of lactate is smaller, i.e. the degree of acidosis less. On the other hand, if 16 per cent. oxygen is breathed, the intake of oxygen during work is smaller and the percentage of the oxygen requirement of the work done incurred as debt is greater; the debt is larger, and therefore the accumulation of lactate must be larger, i.e. the degree of acidosis is greater. In the second place, over the same post-exercise period following work of the same duration and oxygen requirement, the pulmonary ventilation and respiratory quotient are less, and the percentage O_2 absorption and CO_2 excretion are higher when 26 per cent. oxygen is breathed than when air is breathed. On the other hand, if 16 per cent. oxygen is breathed, the ventilation and respiratory quotient are greater, and the percentage O_2 absorption and CO_2 excretion are less, than when air is breathed throughout. Such findings suggest that the degree of acidosis left over at the end of exercise is greater when 16 per cent. oxygen is breathed, and less when 26 per cent. oxygen is breathed, than when air is breathed.

It is arguable, however, that the effect of decreasing the oxygen pressure on the respiratory exchange during exercise is due, partly at least, to consequent anoxaemia causing over-breathing, relative to the requirements of the body for the elimination of carbon dioxide. The causation of the alterations in the respiratory exchange with exercise when air is breathed has already been discussed at some length, and we arrived at the conclusion that anoxaemia could only play a minor part. The part played by anoxaemia when high oxygen pressures are breathed must be smaller still. The part played by anoxaemia when low oxygen mixtures are breathed may well be greater, but that this part is still a minor

one is shown by the fact that the alterations produced in the respiratory exchange by lowering the oxygen percentage in the air breathed to 16 per cent. are not much greater than the alterations produced in the other direction by raising the oxygen pressure to 26 per cent.

Lastly, there remains the question as to how, at the same rate of work, increasing and decreasing the oxygen pressure in the inspired air results in lesser and greater accumulation of lactate respectively. The simplest explanation is to suppose that oxygen pressure acts by increasing or decreasing the oxygen saturation of the arterial blood. During exercise under reduced oxygen pressure, the arterial blood is less fully saturated with oxygen than at rest. Thus, at the end of a week spent in a chamber in which the partial pressure of the oxygen in the atmosphere had been reduced from its sea-level value of 160 to 84 mm. Hg (comparable to an altitude of 18,000 ft.), the percentage saturation of Barcroft's blood dropped from 88.1 at rest to 83.5 when he did work on a bicycle ergometer (5). Similarly, at Cerro in the Andes (15,000 ft.), the oxygen saturation of Meakins' arterial blood dropped from 91 per cent. saturation at rest to 76 per cent. saturation during work (Barcroft (4, p. 72)). Whether the oxygen saturation of the arterial blood is maintained during exercise under ordinary circumstances is uncertain. Himwich and Barr (43) found that the oxygen capacity and oxygen content of the arterial blood invariably rose during exercise, while the oxygen saturation of the arterial blood was actually a little increased. In their experiments, however, work was only continued for about $3\frac{1}{2}$ minutes and at a rate of about 1,000 kilogrammetres (7,000 foot-pounds) per minute. But in an experiment in which Himwich continued running for fourteen minutes, the oxygen saturation of his arterial blood dropped from 98.1 to 92.8 per cent. Harrop (27) made a man work to complete exhaustion in fifteen minutes and found that his arterial blood was only 85 per cent. saturated. The fact that the increased oxygen pressure in the inspired air does increase the maximum oxygen intake of which man is capable certainly suggests that, as the circulation rate through the lungs rises with increasing rate of work under ordinary barometric pressure, the oxygen saturation of the blood is not maintained in spite of compensatory rise in the alveolar oxygen tension. Hill, Long, and Lupton (39) point out that a rich oxygen mixture must act primarily by increasing the oxygen saturation of the arterial blood, as there is no other way in which it could work, but they maintain that the increase in the maximum oxygen intake, when the oxygen pressure in the inspired air is raised, is too great to be explained simply by increased oxygen saturation of the arterial blood. They were driven to conclude that there must be some mechanism by which the heart is able to regulate its output in accordance with the degree of saturation of the arterial blood, so that the circulation is slowed as soon as a serious degree of unsaturation occurs, and vice versa. Hill, Long, and Lupton attribute the accumulation of lactate during work entirely to failure of oxygen supply. But during moderate exercise the oxygen debt is equal to the initial lag in the oxygen intake (Furusawa, Hill, Long, and Lupton (20)); the lactic acid accumulated at the beginning must therefore persist unchanged until

the end. Even during work compatible with the steady state, there must be some rise in the cH of the muscles themselves. Now Hartree and Hill (28) have shown that the rate of oxidative removal of lactic acid in isolated muscle falls off with rise of cH. This initial rise of cH may be, therefore, another factor in limiting the oxygen intake of which a man is capable, and this factor will become a still more important one if Yandell Henderson is right in supposing that the acidosis of muscular exercise is due to other factors besides accumulation of lactate. Decrease in this initial rise of cH during work under high oxygen pressure may therefore be another factor responsible for the increase in the oxygen intake of which a man is capable when working under these conditions.

The alteration in the respiratory exchange during exercise with increase in the pressure of carbon dioxide in the inspired air. During work of the same duration and oxygen requirement, when 5 per cent. carbon dioxide is breathed instead of air, the volume of ventilation required to effect the intake of unit quantity of O_2 and the excretion of unit quantity of CO_2 is greater. Less O_2 is taken out of the same volume of inspired air, and less CO_2 added to it; the alveolar O_2 tension rises, and the alveolar CO_2 tension approximates more closely to the pressure of CO_2 in the inspired air. (See Figs. 12, 13, 17, and 18.) The explanation is obvious. Breathing a CO_2 mixture, more ventilation is required to maintain the necessary difference between the pressure of CO_2 in the venous blood and the pressure of CO_2 in the alveolar air; less O_2 is therefore taken out of the inspired air and the alveolar O_2 tension rises. But breathing 5 per cent. CO_2 the respiratory quotient is lowered, showing that CO_2 produced metabolically is accumulating in the body. That CO_2 produced metabolically can actually be retained in the body during exercise breathing air has been suggested by Campbell, Douglas, and Hobson (11), who supposed that the elimination of this CO_2 so retained is a factor in producing the sudden rise of respiratory quotient which occurs on the abrupt cessation of work. It is possible that the reduction in the O_2 intake of which a man is capable, when he breathes 5 per cent. CO_2 , is due to the consequent carbon dioxide acidosis slowing the rate of oxidation of lactic acid in the muscles.

Summary of Section. The alterations in the respiratory exchange during exercise, when air or other oxygen-nitrogen mixtures are breathed, are chiefly due to lactic acid acidosis. When the composition of the inspired air is kept constant, the degree of acidosis depends upon the rate of work. When the rate of work is kept constant, the degree of acidosis depends upon the extent to which the oxygen pressure in the inspired air is reduced. The alterations in the respiratory exchange during exercise, when the pressure of carbon dioxide in the inspired air is increased, depend upon lactic acid and carbonic acid acidosis.

VI. Theoretical (Physiological): The Limitation of Voluntary Effort.

Voluntary exertion may be conveniently but arbitrarily divided into three types: (1) severe effort of brief duration; (2) slight effort continued over long periods, e. g. industrial occupations; (3) moderate or severe effort continued over

fairly long periods, e.g. the half-mile and three-mile races and intermediate distances. Hill, Long, and Lupton (38) have shown that in severe effort of the first type the muscles themselves are probably stimulated to almost complete exhaustion as in the fatigue of isolated muscle. On the other hand, the fatigue associated with industrial occupations is probably largely of psychological origin. But it is with the limitation of effort of the third type that we are alone concerned, as the work done in our experiments was comparable to middle or long distance track running. There must be two factors in the limitation of effort of this kind, a physical and a psychological. Thus the actual speed at which an athlete can run, say, his fastest mile, or the actual moment at which, in attempting to run it at a certain speed beyond his powers, he has to stop or slow down, must be determined by a combination of the two. During severe muscular exertion it feels as if some physico-chemical 'brake' was being steadily and progressively applied, so that more and more 'voluntary effort' becomes necessary to maintain the same speed of running until eventually the psychological breaking-point is reached. How these physical and psychical factors combine to produce this general subjective feeling of distress (of which respiratory distress—dyspnoea—is only a part) is a problem of psycho-physical interaction which at present it is useless to pursue. As physiologists, all we can hope to do is to discover the nature and cause, and follow the rise, of the physico-chemical change which is one factor in the limitation of voluntary effort.

The classical experiments of physiology have demonstrated that during work of this kind the muscles themselves are not run to complete exhaustion, and that the physico-chemical basis of the fatigue associated with it acts somehow in the central nervous system. As to the actual nature of this physico-chemical change we have no certain information, but it is generally regarded as being in some way associated with cardio-respiratory failure. Thus it might be the direct consequence of oxygen lack. But the athlete runs his race with perfect judgement and is acutely conscious of his distress; there is little to suggest the symptoms which are so characteristic of cerebral anoxaemia. On the other hand, this physico-chemical change may arise primarily in the working muscles, and affect the nervous system via the blood-stream. For instance, it might be accumulation of carbon dioxide, or accumulation of lactic acid, the result of failure of the oxygen supply. But during exercise the symptoms which we have learned to associate with carbon dioxide poisoning are not observed, and Bainbridge (2, p. 187) has pointed out that, as neither lactic nor carbonic acid ever attain sufficient concentration in the body during exercise to be directly toxic, the only possible way in which, so far as it is known, they could affect the nervous system would be by virtue of the rise of hydrogen-ion concentration of the blood which they both produce. Levine, Gordon, and Derick (50) found a marked degree of hypoglycaemia in Marathon runners, and pointed out the similarity between their collapsed condition on finishing and the nervous symptoms of insulin hypoglycaemia. The next year Gordon, Kohn, and others (22) fed many of the same runners on sugar, both before and during the race, and found that

their blood-sugar was much more nearly normal, and showed a correlation between this, their general condition on finishing, and the time they took to complete the course. But, though hypoglycaemia may be a factor in the causation of fatigue during prolonged exertion, it is unlikely that it is important in the limitation of the comparatively short-lived effort of our experiments. During severe exercise, however, the hydrogen-ion concentration of the blood rises progressively, and the rate at which it rises depends upon the rate of work attempted. In the present state of our knowledge it is reasonable to suppose that rise of hydrogen-ion concentration of the blood and tissues is the most important physico-chemical factor in the limitation of voluntary effort of the type under consideration.

When the rate of work is such that the oxygen supply to the muscles begins to fail on account of decreased saturation of the arterial blood or insufficient circulation rate, so that lactate begins to accumulate, the elimination of carbon dioxide from the body will become progressively more difficult, (a) because the CO_2 -carrying power of the blood is progressively reduced, so that an increasing circulation rate is required to transport unit quantity to the lungs, and (b) because with reduced CO_2 -carrying power of the blood more and more pulmonary ventilation is required to eliminate unit quantity. But under these circumstances there is an increasing demand for the elimination of carbon dioxide in excess of that produced by metabolism, to keep down the rising hydrogen-ion concentration of the blood. On the other hand, accumulation of lactate and rise of eH of the blood does not interfere with the supply of oxygen to the tissues, but rather does the reverse. Rise of eH lowers the oxygen dissociation curve of blood, increases the rate of dissociation of oxyhaemoglobin, and decreases the rate of oxidation of haemoglobin (Barcroft (3)); at any given low oxygen pressure in the tissues oxyhaemoglobin dissociates both more completely and more rapidly. It is true that in the lungs, at any given oxygen pressure, the oxidation of haemoglobin will now be less complete and less rapid, but this is compensated for by the increased ventilation and the raised alveolar oxygen pressure; in addition, during exercise the oxygen capacity of the arterial blood is increased.

We therefore maintain that carbon dioxide elimination as well as oxygen supply must be an important factor in determining the amount of work of which a man is capable. Moreover, if reduction in the CO_2 -carrying power of the blood is due to other factors besides the accumulation of lactic acid (Yandell Henderson), then difficulty in effecting the excretion of carbon dioxide from the body is likely to be a still more important factor, as it will come into action earlier, i.e. before the limit of the steady state of exercise has been reached. The mechanism of the limitation of voluntary effort is therefore more complicated than if it depended on failure of oxygen supply alone, and particularly as our experiments suggest that an interrelationship exists between the cardio-respiratory mechanisms for oxygen intake and carbon dioxide output respectively.

Our conception of the limitation of voluntary effort is that it is something like this. When the rate of work is such that the oxygen supply to the muscles fails

to meet the demand for oxygen supply, so that lactate accumulates, the cH of the blood must rise steadily to the point at which voluntary effort ceases, not only on account of the accumulation of lactic acid as the mechanism for oxygen intake fails, but also on account of the accumulation of carbonic acid as the mechanism for the elimination of carbon dioxide fails. Available base will now be divided between these two acids, with the liberation of equivalent quantities of weaker buffer acid to which the actual rise in cH of the blood and tissues will be due. But as lactate accumulates, this partition of base is shifted progressively in favour of lactic acid, so that less and less becomes available to carry CO_2 . A greater circulation rate and minute volume of ventilation will now be required to eliminate unit quantity. Less O_2 will therefore be taken out of the inspired air, and the alveolar O_2 pressure will rise. This, however, by increasing the O_2 saturation of the arterial blood (or by whatever method increased O_2 pressure does exert its effect) will tend to decrease the accumulation of lactate, and so make the elimination of CO_2 easier. Less ventilation will now be required to eliminate unit quantity of CO_2 , and more O_2 will be taken out of the inspired air. The alveolar O_2 tension will therefore fall again, and so on, with the result that as work progresses and lactic acid accumulates, a balance will be maintained between the capacities of the mechanisms for oxygen intake and carbon dioxide output respectively. As one is reduced, the other is reduced correspondingly. The limits of the capacities of the two mechanisms will probably be reached simultaneously.

As lactate accumulates, progressive increase in the volume of pulmonary ventilation is necessary, not only to maintain the oxygen saturation of the arterial blood as the circulation rate rises, but also to effect the elimination of carbon dioxide as the CO_2 -carrying power of the blood becomes reduced. In the same way, progressive increase in the circulation rate is necessary, not only to maintain the elimination of carbon dioxide as the CO_2 -carrying power of the blood is reduced, but also to maintain the oxygen supply to the muscles, as the O_2 saturation of the arterial blood falls. Circulation and ventilation are therefore each just as essential, in respect both of oxygen intake and carbon dioxide output. Just as the mechanisms for oxygen intake and carbon dioxide output probably fail together, so too it is likely that circulation and ventilation will prove inadequate at about the same time.

Now breathing a high oxygen mixture enables a man running 'all out' to incur a larger oxygen debt, and so do more work than would have been possible if only air had been breathed. This conception of the limitation of voluntary effort, which takes into account the difficulties of CO_2 elimination as well as those of O_2 supply, affords a possible explanation of this fact on the basis of rise of cH alone, instead of having to postulate anoxaemia as another physico-chemical factor in the production of the subjective distress which limits muscular effort. Raising the oxygen pressure in the inspired air, by increasing the oxygen supply to the muscles, delays the accumulation of lactate, and so makes the elimination of carbon dioxide easier. Retention of CO_2 is therefore delayed, and, for the

same limiting rise of cH , therefore, at which voluntary effort ceases, a greater accumulation of lactate is possible; i. e. a larger O_2 debt can be incurred and a greater rate of work accomplished. On the other hand, lowering the oxygen pressure in the inspired air may act, not by making the individual more intolerant of rise of cH , but by decreasing the oxygen supply to the working muscles, and so accelerating the accumulation of lactate, and making the elimination of carbon dioxide more difficult. Retention of CO_2 would then be hastened, and, for the same limiting rise of cH , the accumulation of lactate would be smaller; i. e. a smaller O_2 debt is all that can be incurred, so that less work can be done. Breathing 5 per cent. carbon dioxide reduces the amount of work a man can do, partly by decreasing the magnitude of the oxygen debt that he can incur. The explanation of this on similar lines would be that the consequent CO_2 acidosis shifts the partition of available base in favour of carbonic acid, so that at the same final hydrogen-ion concentration at which voluntary effort ceases the accumulation of lactate is smaller and the O_2 debt incurred is less.

The conception of the limitation of voluntary effort which we have attempted to outline depends not only on the capacity of the mechanism for the intake of oxygen, but also on that of the mechanism for the elimination of carbon dioxide, and on the interrelationships which exist between them. That reciprocal relationships exist between the oxidation of haemoglobin and the evolution of carbon dioxide in the lung, and again, between the dissociation of oxyhaemoglobin and the evolution of carbon dioxide from the tissues, is well established; that a similar reciprocal relationship should exist between the mass intake of oxygen and the mass output of carbon dioxide during muscular exercise is probable. This conception is admittedly theoretical, but as some conception of the mechanism of the limitation of voluntary effort is essential in the clinical study of heart disease, it has been advanced as an alternative to the simpler idea that it depends chiefly on circulation rate and on oxygen supply alone; it is believed to be one which will explain the observations of clinical medicine more satisfactorily.

Summary of section. The physico-chemical factor in the limitation of voluntary effort is rise of hydrogen-ion concentration of the blood and tissues. During severe muscular exertion the hydrogen-ion concentration rises progressively: (a) due to accumulation of lactic acid as the mechanism for oxygen intake fails, and (b) due to the accumulation of carbonic acid as the mechanism for the elimination of carbon dioxide fails. The limitation of voluntary effort is set by the eventual failure of the cardio-respiratory system as a whole; by simultaneous failure of circulation and ventilation, and simultaneous failure of oxygen intake and carbon dioxide output, to prevent rise of hydrogen-ion concentration to the point at which voluntary effort ceases.

VII. Theoretical (Clinical): The Mechanism of Heart Failure.

After this excursion into the domain of pure physiology, we return to the clinical problem, which we attempted to outline in the introduction to this paper,

namely, the functional pathology of the transition between normal health and death by cardiac failure. As the result of our experimental work we have come to the conclusion that the limitation of voluntary effort is determined by the eventual failure of the whole cardio-respiratory system, heart, lungs, and blood, to prevent gradual rise of hydrogen-ion concentration, the most important physico-chemical factor responsible for the subjective distress which ultimately limits voluntary muscular exertion. This rise of hydrogen-ion concentration is due to the combined effect of the accumulation of lactic acid as the mechanism for oxygen intake fails, and the accumulation of carbonic acid as the mechanism for carbon dioxide elimination fails. Moreover, the limitation of voluntary effort probably depends on simultaneous failure of circulation and ventilation, and, in addition, the cardio-respiratory mechanisms for oxygen intake and carbon dioxide output are so interrelated that, as this point is reached, oxygen supply and carbon dioxide elimination probably fail together. Also, during the most intense exertion, the minute output of the heart is adequate to cope with the venous return, which largely depends on the respiratory movements and the contractions of the working muscles. The limitation of voluntary effort, therefore, does not depend on failure of one organ before another, circulation before ventilation; it does not depend on premature failure of one function, oxygen supply before carbon dioxide elimination; nor does it depend on failure of the heart to keep pace with the venous return.

The work of Sir Charles Sherrington (82) on the physiology of the nervous system has made it clear that, from the physiological point of view, evolution is to be regarded as the progressive specialization and differentiation of function into certain groups of cells or organs in the body, and the simultaneous integration or co-ordination of the functional activity of these organs, so that the requirements of the body as a whole are most efficiently served. This is a general biological principle, more apparent perhaps in the nervous system than elsewhere, but nevertheless applicable to the body as a whole. Thus it may be said that the functional activity of the heart, blood, and lungs is integrated so that the respiratory needs of the tissues may be most efficiently served. We would now restate our conclusion in these terms. The limitation of voluntary effort is determined by the eventual failure of the integrated activity of the cardio-respiratory system as a whole, by simultaneous failure of circulation and ventilation, by simultaneous failure of oxygen supply and carbon dioxide elimination, and by simultaneous failure of cardiac output and venous return. During extreme muscular exertion integration of all the functional activities of the body concerned is maintained, and *dis-integration* of cardio-respiratory function does *not* supervene.

But what happens to the integration of cardio-respiratory functions in organic heart disease? Let us start with an analogy. Suppose eight men by going 'all out' are able to row their boat a certain distance in a certain time. Imagine that half-way down the course No. 4 of the crew breaks his stretcher. No. 4 will now be suffering from a severe mechanical handicap to his rowing, and if he is to continue rowing with the same expenditure of energy as

before, he must now either shorten his stroke or reduce his rate of striking. In either case the boat as a whole will be thrown into confusion, and the co-ordinated integrated activity of the eight men is lost; the course is not completed. But such a break-down could have been avoided if stroke had compensated, when the accident occurred, by reducing his rate of striking to an extent that would just permit of No. 4 continuing to row. The course would now have been completed, but in slower time. No. 4 would have been rowed 'right out', but the rest of the crew would have been left with some reserve in hand. Now suppose a man is able by running himself 'all out' to run a certain distance in a certain time. According to our conception of the limitation of effort, the rate at which he can run this distance will be determined by the ability of his cardio-respiratory system as a whole to keep down the rising hydrogen-ion concentration of his blood. Now one of the peculiarities of pathological processes is that they frequently attack one organ and interfere with one function of the body, leaving the other organs and other functions still intact. A good example, and one with which we are particularly concerned, is chronic rheumatic infection of the heart. Suppose, therefore, that this man develops chronic rheumatic heart disease, and that the cardiac lesion is not completely compensated for by hypertrophy as is usually the case, as is shown by the progressive limitation of effort of which such a patient would complain. He now has a heart the functional efficiency of which is reduced (comparable to the oarsman with the broken stretcher) relative to the functional capacity of the other members of his cardio-respiratory system (the other members of the crew). Now let him attempt to run the same distance in the same time. The same circulation rate will be demanded, but it will be one which his diseased heart cannot meet; clearly he will not 'complete the course'. Up to a certain point increased ventilation may compensate for insufficient circulation rate. But beyond a certain point, increase in pulmonary ventilation cannot appreciably increase the oxygen saturation of the arterial blood, although it may be more than adequate to effect the necessary elimination of carbon dioxide. Over-ventilation beyond this point is likely to occur (as the stimulus to the respiratory centre will probably be excessive), but it will serve no useful purpose. Rather it will tend to increase the venous return to a rate with which the diseased heart can no longer cope. The blood will now accumulate in the veins, and this will lead to oedema of the lungs, and then to all the symptoms of congestive cardiac failure. The man under consideration will therefore be pulled up, not by the ordinary mechanism of the limitation of voluntary effort, failure of integrated cardio-respiratory activity, but because *dis-integration* of cardio-respiratory function has supervened; circulation has now failed before ventilation, oxygen supply before carbon dioxide elimination, and cardiac output before venous return.

But the fact remains that in compensated heart disease congestive cardiac failure does not supervene on attempted effort, and there must therefore be some reason why such a patient is pulled up in the ordinary way before the break-down, cardio-respiratory dis-integration, which we have been led to anticipate, actually occurs. So long as the excessive stimulus to ventilation is present, as is likely

to be the case, this can only be explained by supposing that there is a reduction in the capacity of the patient to effect pulmonary ventilation to about the same corresponding degree as the reduction in the capacity of his heart to effect cardiac output. If such a mechanism existed, it would then happen that on attempted effort the different cardio-respiratory functions would all fail together, so that dis-integration of cardio-respiratory function, heart failure, would not supervene. Is there, therefore, any evidence that, when the functional capacity of the heart is reduced by disease, the ability to effect pulmonary ventilation is correspondingly reduced, although the lungs themselves are not diseased?

Peabody (62, 63, 64) employed rebreathing with consequent progressive increase in the percentage of carbon dioxide in the inspired air as a functional test of ventilation. Normal subjects were found to increase their ventilation eight times before the breaking point was reached. Patients with compensated heart disease responded in exactly the same manner as normal men to rise in the percentage of carbon dioxide in the inspired air, in the sense that the same rise in CO_2 percentage produced the same percentage increase in pulmonary ventilation, but they were unable to increase their ventilation to more than about three times the normal. Extreme dyspnoea was therefore produced more quickly, the breaking point was reached much sooner, and the rise of percentage of CO_2 in the inspired air which they could tolerate was less than in normal men. Peabody concluded that cardiac patients became dyspnoeic sooner than normal subjects, not because the respiratory centre was more sensitive to the same stimulus, but because they were unable to meet the rising stimulus to respiration with adequate increase in ventilation, and that limitation of the depth of breathing is an important factor in the production of dyspnoea in patients with cardiac disease. Peabody and Wentworth (67) were therefore led to a detailed study of the vital capacity in normal subjects and in patients with cardiac disease. Determinations of the vital capacity of the lungs in a large number of healthy persons made it possible to establish average normal standards for groups of individuals of different sex and height. When compared to the proper standard, the vital capacity of healthy persons very seldom fell below 90 per cent. of the normal, although—especially in trained athletes—it was frequently well above normal. On the basis of vital capacity they divided their cardiac patients into four groups.

Group I. Vital capacity of 90 per cent. of the normal. These patients did not usually complain of cardiac symptoms, and in the majority the cardiac lesion had been discovered accidentally.

Group II. Vital capacity of 70–90 per cent. of the normal. These patients complained of breathlessness on exertion, but about half were at work, and the majority were able to lead satisfactory though somewhat restricted lives.

Group III. Vital capacity of 40–70 per cent. of the normal. Patients with vital capacities of 40–45 per cent. of the normal were invariably in bed, dyspnoeic at rest or on the least exertion. Those with a vital capacity of 45–60 per cent. of the normal were rarely dyspnoeic in bed, and most could walk slowly round the ward without becoming unduly short of breath. Those with a vital capacity

of 60-70 per cent. of the normal could usually attend the hospital as out-patients, and walk up a flight of stairs without special distress.

Group IV. Vital capacity below 40 per cent. These patients were bed-ridden and severely decompensated, and those with a vital capacity below 30 per cent. of the normal had extreme dyspnoea and orthopnoea. The lowest vital capacity recorded was 17 per cent. of the normal.

Peabody and Wentworth (67) and Maclure and Peabody (58) have also described a close correlation between change in vital capacity and the clinical condition of the patient. Progressive heart failure was found associated with a gradual reduction in the vital capacity, and the slow return to compensation with a progressive increase in the vital capacity. Experiments were also performed to show that reduction in vital capacity is a real phenomenon, and not merely due to an imperative stimulus to inspire developing before expiration was complete; thus they found that even their patients with the lowest vital capacities could still hold their breath for several seconds after a maximum inspiration or expiration. Sturgis, Peabody, and others (83) have also shown that the maximum volume of ventilation that normal subjects and cardiac patients can sustain is proportional to their vital capacity in both cases.

Peters and Barr (74, 75, 76) have also investigated the functional capacity of ventilation in cardiac patients, and confirmed many of Peabody's observations. They showed that the vital capacity is reduced in cardiac patients, and that this is not due to an increase in the residual air at the end of a maximal expiration; that the maximum volume of the tidal air attained under the rising stimulus of continuous rebreathing is lower in patients with cardiac dyspnoea than in normal subjects; that the reduction in the maximal tidal air bears a close relationship to the reduction in vital capacity; and that such patients are therefore unable to stand the same percentage of CO_2 in the inspired air as normal men. Peters (72, 73) and Peters and Barr (77, 78) also showed that the alveolar CO_2 percentage is usually reduced in patients with cardiac dyspnoea (thus confirming the observations of a number of other workers), and also that the tension of CO_2 in the alveolar air is invariably reduced relative to the venous plasma bicarbonate as compared with normal men. They point out that it is the low percentage of CO_2 in the effective alveolar air which makes the increased ventilation of patients with cardiac dyspnoea essential, and that it is the diminished effective lung volume and the consequent reduction in 'the reserve of the mechanical apparatus of respiration that makes any large increase in ventilation difficult or impossible'. (For further literature on this subject, *vide* Myers (60).)

Reduction in the capacity of the patient to effect pulmonary ventilation, therefore, may well be the reason why cardio-respiratory dis-integration, i. e. congestive cardiac failure, does not supervene when patients with compensated heart disease and limitation of effort run themselves to complete exhaustion. The actual cause of the reduction in the vital capacity in heart disease, and the corresponding reduction in the ability to effect pulmonary ventilation, is uncertain. We would emphasize, however, that it makes *no difference whatever how this is brought*

about, whether it is due to venous congestion in the lung, or whether it is brought about by reflex action. By whatever mechanism it is produced, it will serve the purpose of a protective reaction to reduce the amount of work of which the man is capable, and thus ensure that he will be pulled up in the ordinary way before a rate of work is attempted which would inevitably lead to congestive cardiac failure. But to a protective reaction of this kind there must be a limit, and when this limit is reached, dis-integration of cardio-respiratory function, heart failure, will supervene on attempted effort, and later will be present even at rest. In clinical medicine this state of affairs is most obvious in the hyperpnoea and stagnant anoxaemia of the very last stages of heart failure. The excessive ventilation is serving no useful purpose in consequence of the gross reduction in circulation rate. In this condition morphia, which depresses the breathing, is well known to improve the clinical condition of the patient.

We have therefore arrived at the conclusion that, from the standpoint of physiology, heart disease must be looked upon from the point of view of progressive dis-integration of cardio-respiratory function which it tends to produce, and from the point of view of the functional adaptations by which, under these circumstances, integration of cardio-respiratory function is for a time maintained. This is admittedly teleological, more teleological perhaps than will be generally acceptable, but no more so, it is maintained, than toxin and antitoxin, acclimatization to high altitudes, or the simple fact of cardiac hypertrophy. Just as it is in the nervous system that integration of function is most obvious, so again it is in the nervous system that dis-integration of function is most apparent. But in the heart itself we get simple instances; for example, the complete dis-integration of auricular and ventricular function in auricular fibrillation or complete heart-block. In the cardio-respiratory system the same principle must still apply, although the steps are so much more complex. We are prepared to admit that this conception of dis-integration of function in heart disease is rather abstract, but Whitehead (84) has written: 'The paradox is now fully established that the utmost abstractions are the true weapons with which to control our thought of concrete facts.' We think, therefore, that something is to be gained from the point of view which we have attempted to elaborate, particularly as it may have an application in general clinical medicine, as well as in the particular field of cardiology.

Physiologists, largely by studying the functions of isolated organs and tissues, are attempting to piece together the different parts, and so gradually synthesize the complete functional picture of man with all the co-ordinating mechanisms, on which his perfect integration of function depends. But clinicians and pathologists are of necessity studying physiology by a different method. Starting with the normal man, they watch the progressive dis-integration of function produced by disease. This is no passive process. As the functional activity of this or that organ becomes reduced, integration is for a time maintained by the re-adaption of the functions of other organs in relation to those that are diseased. For a time, and often for a long time, these attempts are

successful, but ultimately dis-integration of function begins, and at death becomes complete. If this is so, then the central problems in the science of functional pathology are the study of the mechanisms by which in disease integration of bodily function is maintained, and the separation of the functional changes seen in disease into those which are (a) the direct result of the disease process itself, (b) part of the process by which integration of function is preserved, and (c) actual manifestation of *dis-integration* of function itself.

VIII. Summary.

1. The limitation of voluntary effort is usually said to depend on failure of the cardio-respiratory system, more particularly the heart, to effect further oxygen supply to the working muscles. Failure to excrete carbon dioxide seems hardly to have been considered as a possible factor in the determination of the rate of work of which a man is capable.

2. The symptomatology of extreme muscular exhaustion is not comparable with that of congestive heart failure. Congestive heart failure is characterized by accumulation of blood in the venous system, but this does not occur during severe muscular effort in the normal man. The normal heart is capable of dealing with the venous return of the most intense effort. In heart failure the diseased heart is unable to cope with the venous return under resting conditions.

3. The respiratory exchange in normal men has been investigated at increasing rates of work over the same period of time breathing (a) air, (b) 26 per cent. oxygen, and (c) 16 per cent. oxygen at prevailing barometric pressure.

4. With increasing rate of work (increasing oxygen requirement) the volume of pulmonary ventilation required to effect the intake of unit quantity of oxygen and the excretion of unit quantity of carbon dioxide rises progressively. With increasing rate of work less and less oxygen is taken out of the same volume of inspired air, and less and less carbon dioxide added to it; the alveolar O_2 tension rises, and the alveolar CO_2 tension falls. The percentage of oxygen requirement incurred as debt increases.

5. During work of the same duration and oxygen requirement, when 26 per cent. oxygen is breathed instead of air, the volume of ventilation required to effect the intake of unit quantity of oxygen and the excretion of unit quantity of carbon dioxide is less. More oxygen is taken out of the inspired air, and more carbon dioxide added to it; the O_2 tension in the alveolar air approximates less closely to the O_2 pressure in the inspired air, and the alveolar CO_2 tension rises. The percentage of oxygen requirement incurred as debt is smaller.

6. During work of the same duration and oxygen requirement, when 16 per cent. oxygen is breathed instead of air, the volume of pulmonary ventilation required to effect the intake of unit quantity of oxygen and the excretion of unit quantity of carbon dioxide is greater. Less oxygen is taken out of the inspired air, and less carbon dioxide added to it; the alveolar O_2 pressure approximates

more closely to the pressure of O_2 in the inspired air, and the alveolar CO_2 tension falls. The percentage of oxygen requirement incurred as debt is greater.

7. The cause of these alterations in the respiratory exchange is discussed. They are attributed to increasing lactic acid acidosis with consequent progressive reduction in the CO_2 -carrying power of the blood. The degree of acidosis depends, not only on the rate of work, but also on the composition of the inspired air. At the same rate of work, raising the oxygen pressure in the inspired air decreases, and lowering the oxygen pressure in the inspired air increases, the degree of lactic acid acidosis.

8. When the rate of work is such that the oxygen supply to the muscles fails, so that lactic acid begins to accumulate, the elimination of carbon dioxide becomes progressively more difficult, (a) because the CO_2 -carrying power of the blood is reduced, and (b) because more pulmonary ventilation is now required to eliminate unit quantity, while more CO_2 must now be eliminated to keep down the rising hydrogen-ion concentration of the blood.

9. The physico-chemical factor in the production of the subjective distress, which limits voluntary effort, is rise of hydrogen-ion concentration of the blood and tissues. During severe muscular exertion the hydrogen-ion concentration rises progressively, (a) due to accumulation of lactic acid as the mechanism for oxygen intake fails, and (b) due to the accumulation of carbonic acid as the mechanism for the elimination of carbon dioxide fails. The limitation of voluntary effort is set by the eventual failure of the cardio-respiratory system to prevent rise of hydrogen-ion concentration to the point at which voluntary effort ceases.

10. The limitation of voluntary effort is determined by the eventual failure of the integrated activity of the cardio-respiratory system as a whole, i. e. by simultaneous failure of circulation and ventilation. The cardio-respiratory mechanisms for oxygen intake and carbon dioxide output respectively are so interrelated to each other that, as this point is reached, oxygen supply and carbon dioxide elimination fail together. Moreover, during intense exertion the cardiac output of which the heart is capable is still adequate to cope with the venous return.

11. During extreme muscular exertion *dis-integration* of cardio-respiratory function does *not* supervene. That is to say, one organ does not fail before another, circulation before ventilation; one function does not fail prematurely, oxygen intake before carbon dioxide output; the cardiac output does not fail to keep pace with the venous return.

12. From the physiological standpoint heart disease is to be looked upon from the point of view of progressive *dis-integration* of function. As the functional efficiency of the heart is reduced by disease, integration of cardio-respiratory function is for a time maintained by a corresponding reduction in the functional capacity of the mechanical apparatus for breathing. When the limits of this protective reaction are reached, *dis-integration* of cardio-respiratory function begins; circulation now fails before ventilation, oxygen intake before carbon dioxide

elimination, and cardiac output before venous return. Then alone do the symptoms of congestive cardiac failure supervene.

In conclusion, we have to acknowledge our indebtedness to a number of friends. Thomas Lant, Esq., J.P., generously defrayed the whole expense of our apparatus. To Professor Arthur Ellis we are indebted for the encouragement we have derived from his continued interest in our work. Dr. Maitland Jones co-operated with us in our unpublished experiments on cardiac patients, and assisted us in fitting up our apparatus; in this connexion the mechanical ingenuity of Mr. H. S. Souttar, F.R.C.S., proved invaluable. Mr. H. N. Bradbrooke, M.B., was associated with us in our early work, but a ski-ing accident unfortunately deprived us of his further co-operation. Mr. V. H. Brink, M.B., has assisted us with a number of the experiments. Lastly, we wish to express our sincere thanks to our experimental subjects, students of the London Hospital, without whose cheerful co-operation this work would not have been accomplished.

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For explanation of diagrams, see page 394.



FIG. 1. General view of apparatus. A. Bag containing mixture to be inspired. c. Small bags for collection of expired air. D. Apparatus for collection of alveolar air. E. Large bag for collection of debt.

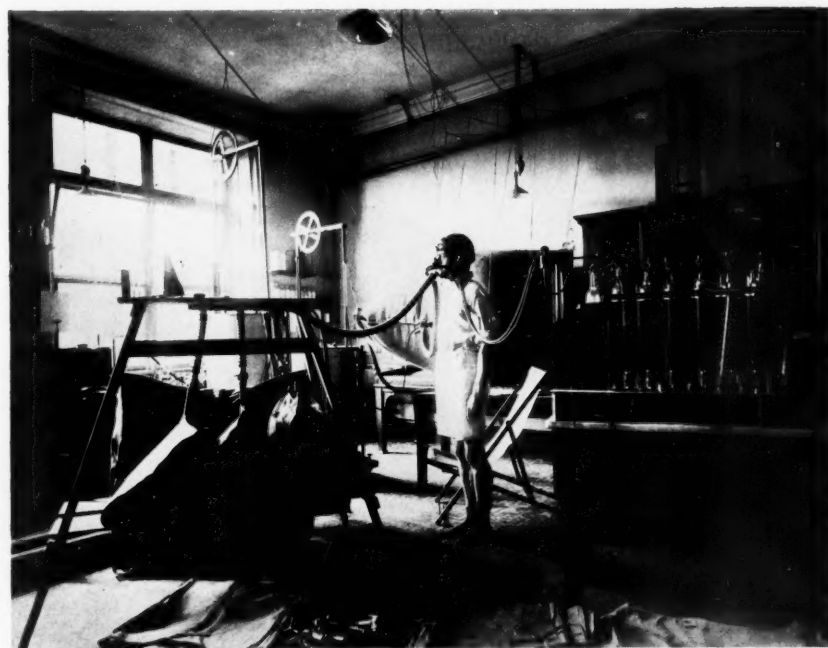
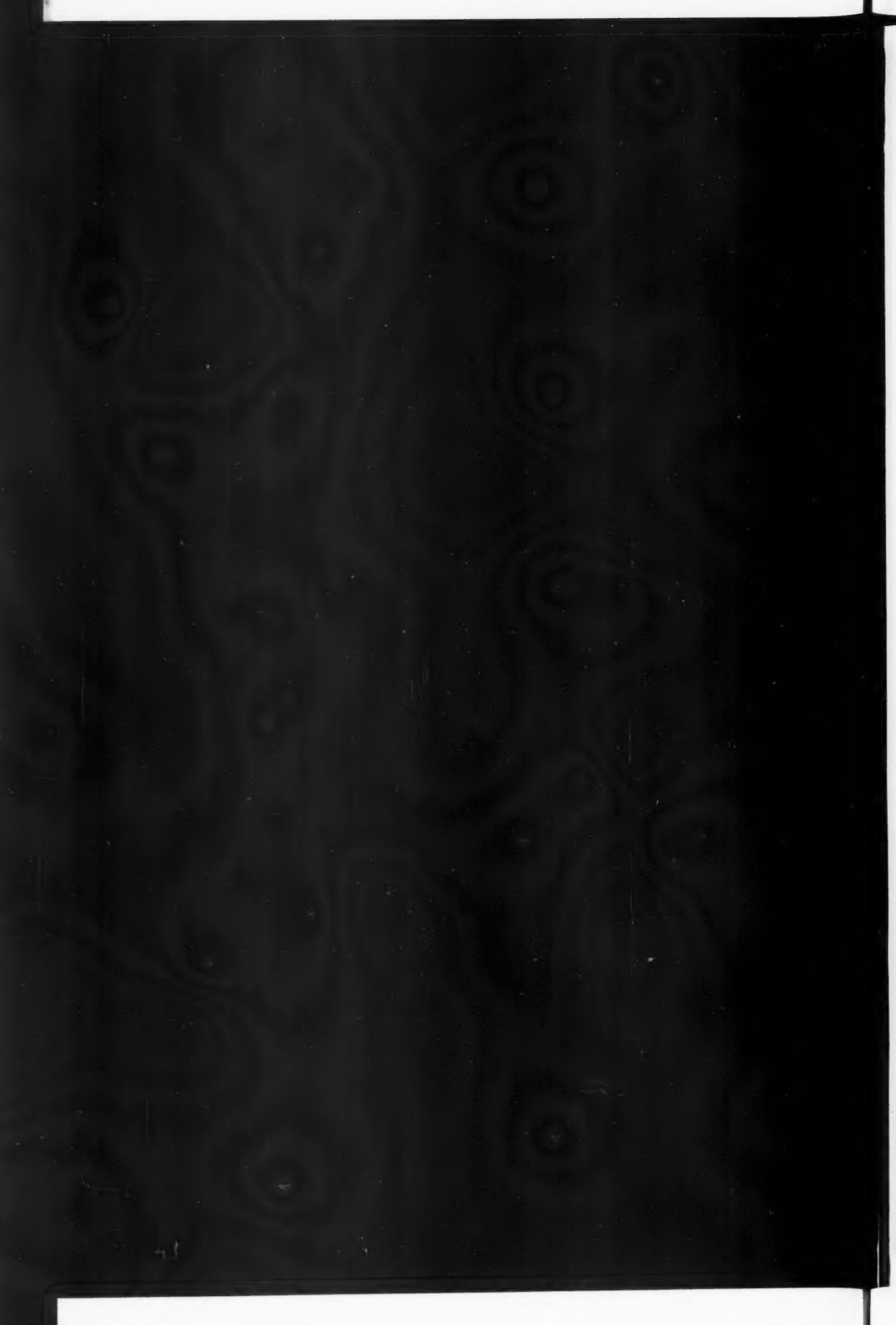


FIG. 2. General view of apparatus.



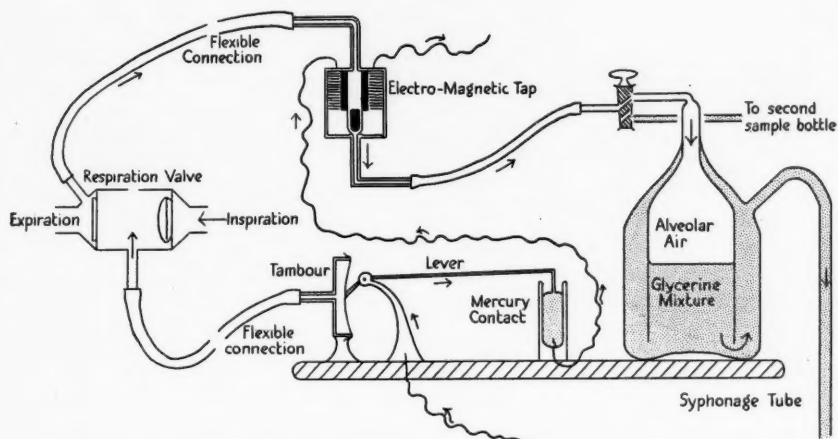


FIG. 3. The apparatus for the collection of alveolar air during exercise (diagrammatic), (see p. 391).

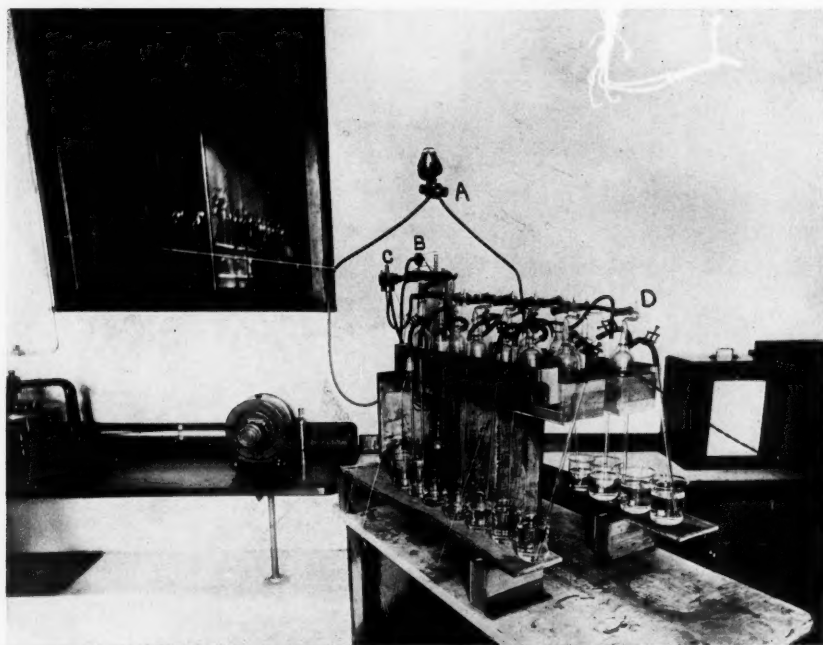


FIG. 4. The apparatus for the collection of alveolar air during exercise (see p. 391).
A. Breathing valve. B. Tambour and lever. C. Electro-magnetic tap. D. Sample bottles.

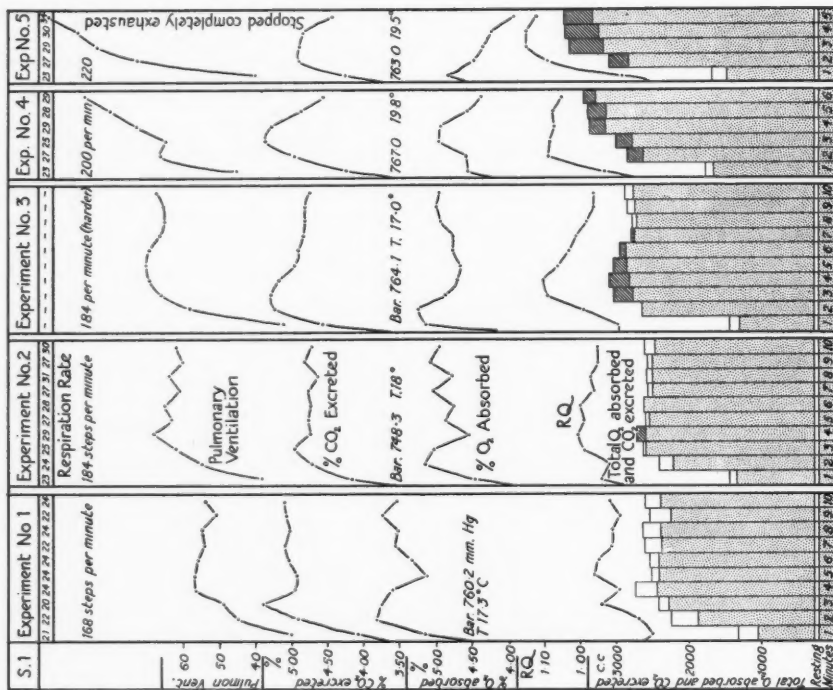


Fig. 5. Subject No. 1. The respiratory exchange at increasing rates of running.

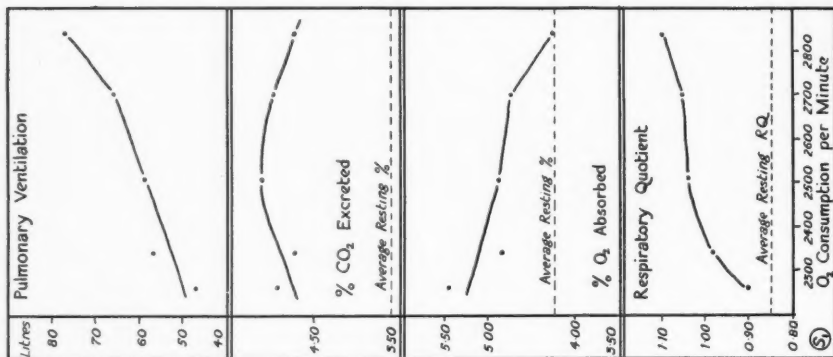


Fig. 6. Subject No. 1. 'Totals', calculated for the first five minutes of all experiments, plotted against the average oxygen consumption per minute (see p. 895).

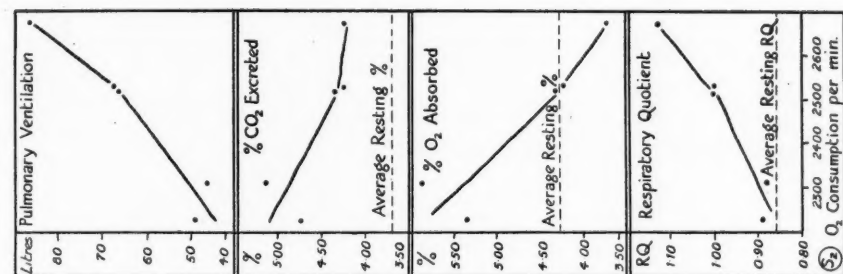


Fig. 8. Subject No. 2. 'Totals', calculated for the first 5 minutes of all experiments, plotted against average oxygen consumption per min. (see p. 395).

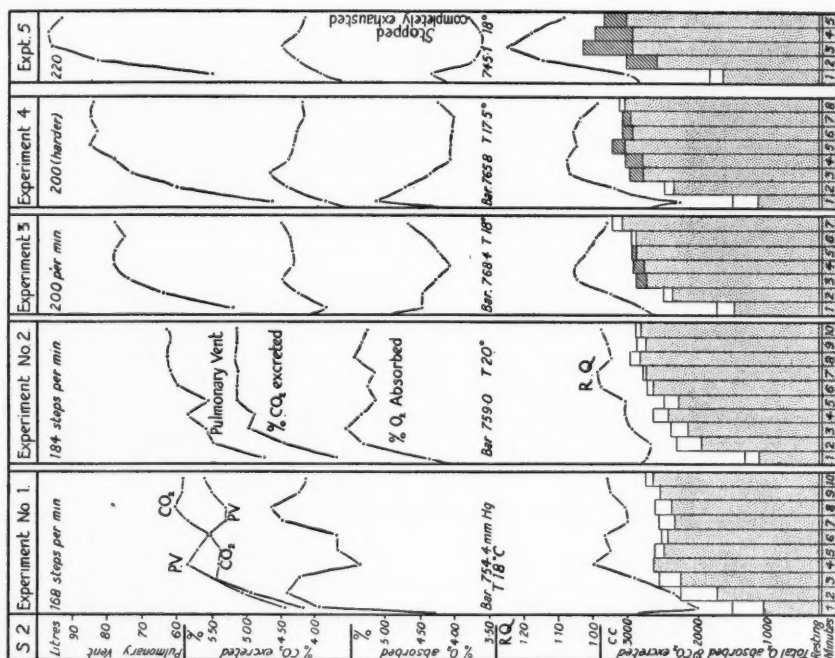


Fig. 7. Subject No. 2. The respiratory exchange at increasing rates of running.

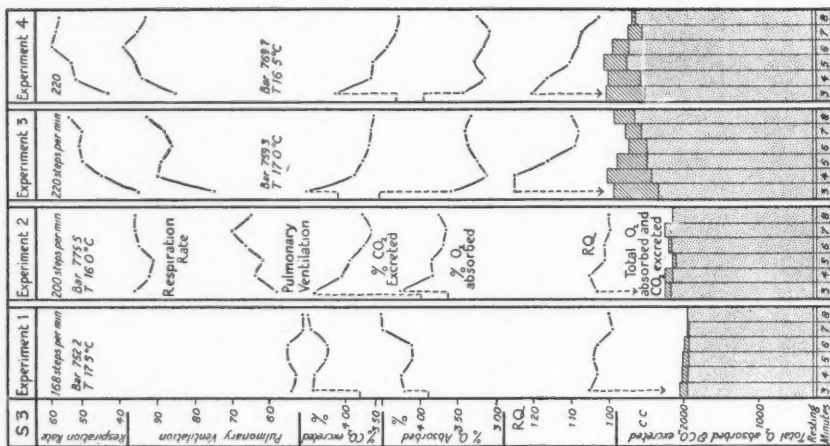


Fig. 9. Subject No. 3. The respiratory exchange at increasing rates of running.

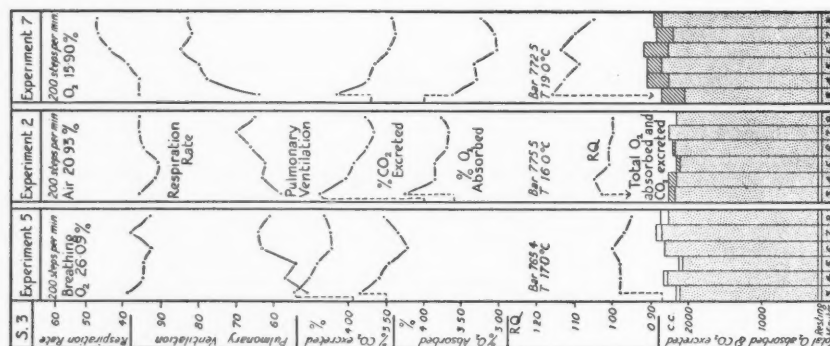


Fig. 10. Subject No. 3. The respiratory exchange during running at 200 steps per minute, breathing 16% O₂ air (21% O₂), and 26% O₂.

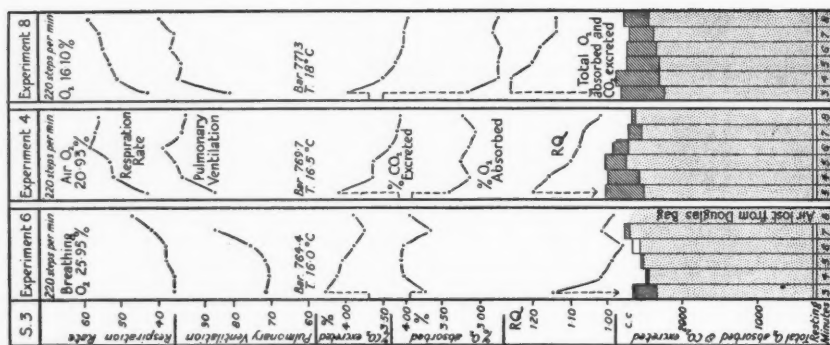


Fig. 11. Subject No. 3. The respiratory exchange during running at 220 steps per minute, breathing 26% O₂ air (21% O₂), and 16% O₂.

(21 % O_2), and 20 % O_2 .

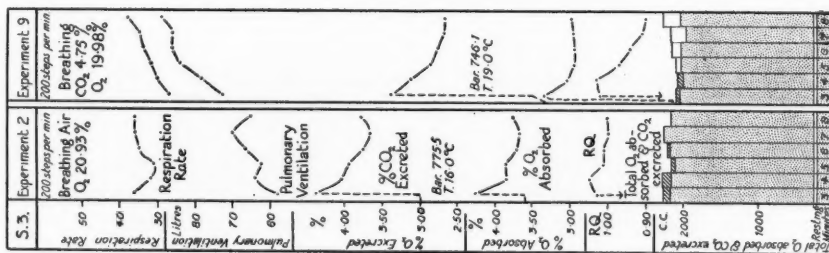


FIG. 12. Subject No. 3. The respiratory exchange during running at 200 steps per minute, breathing air, and then 5 % CO_2 .

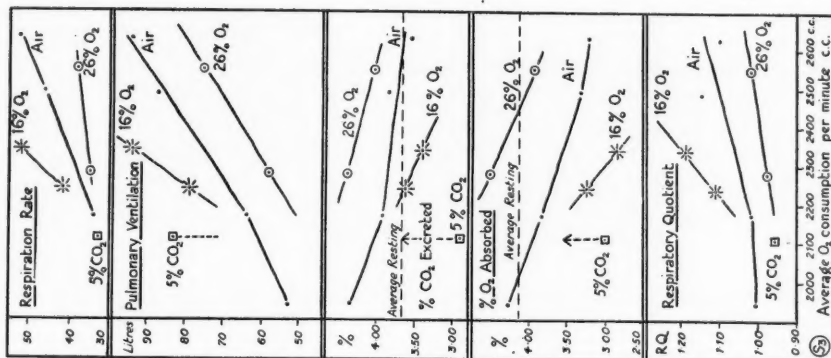


FIG. 13. Subject No. 3. 'Totals' calculated for the whole work period of all experiments, plotted against average oxygen consumption per minute. Experiments in air dots, 26 % O_2 circles, 16 % O_2 stars, 5 % CO_2 squares (see p. 395).

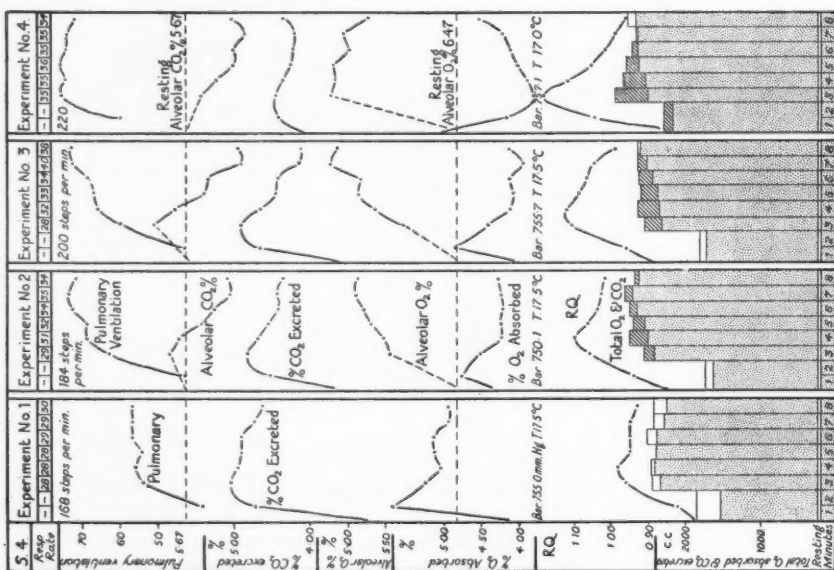


Fig. 14. Subject No. 4. The respiratory exchange at increasing rates of running.

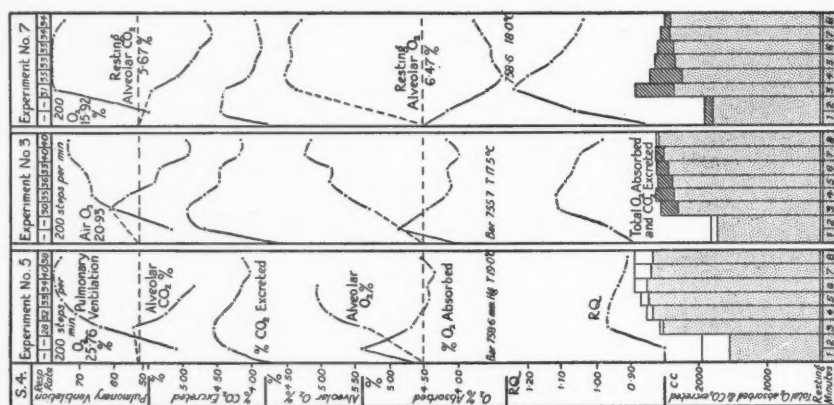


Fig. 15. Subject No. 4. The respiratory exchange during running at 200 steps per minute, breathing 26% O_2 , air (21% O_2), and 16% O_2 .

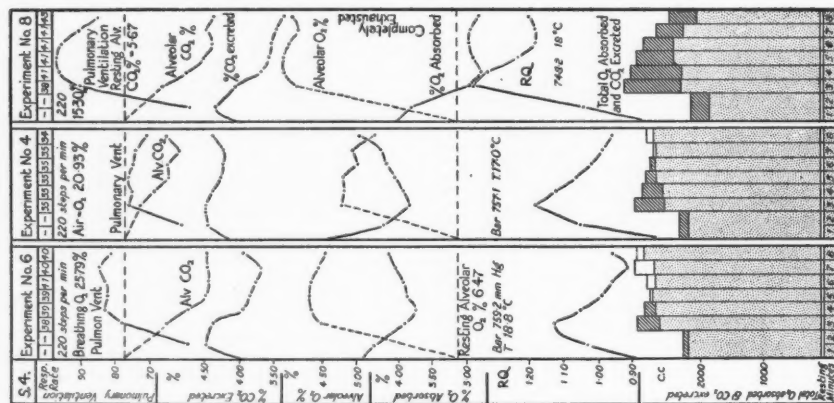


Fig. 16. Subject No. 4. The respiratory exchange during running at 220 steps per minute, breathing 26% O_2 , air (21% O_2), and 16% O_2 .

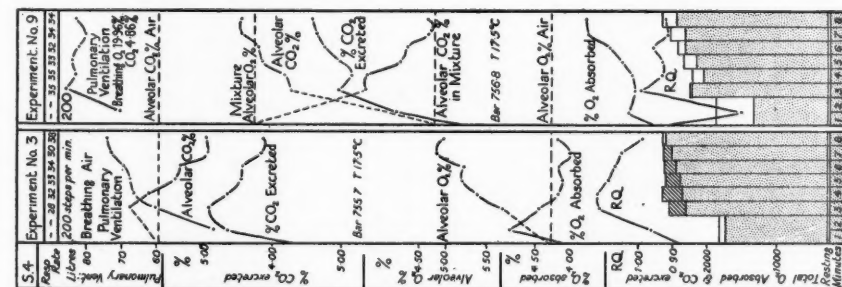


Fig. 17. Subject No. 4. The respiratory exchange during running at 200 steps per minute, breathing air, and then 5% CO_2 .

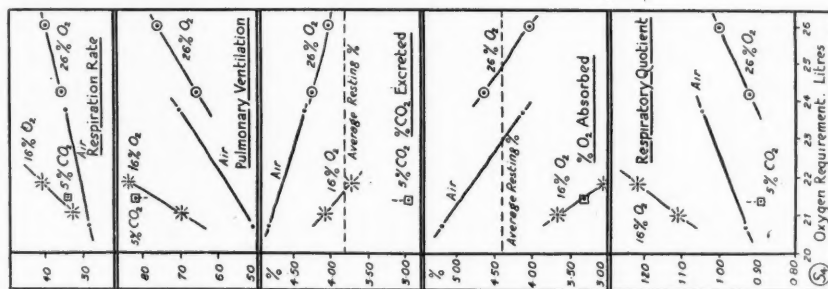


Fig. 18. Subject No. 4. 'Totals', calculated for the whole work period in all experiments, plotted against oxygen requirement.

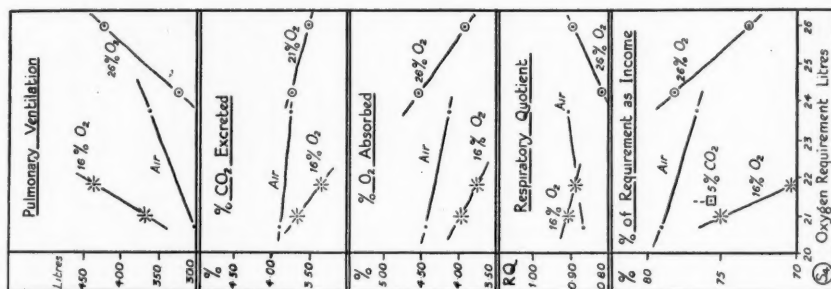


Fig. 19. Subject No. 4. 'Totals', calculated for the recovery period (30 minutes) in all experiments, plotted against oxygen requirement. Lowest diagram partition of O_2 requirement between income and debt.

Experiments in air dots, 26% O_2 circles, 16% O_2 stars, 5% CO_2 squares (see p. 395).

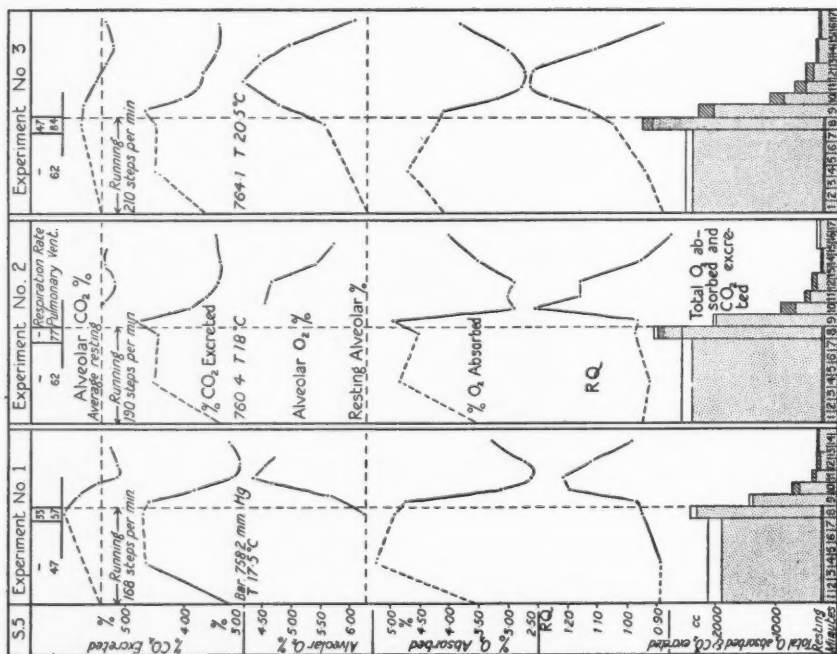


Fig. 20. Subject No. 5. The respiratory exchange during and after running at increasing rates.

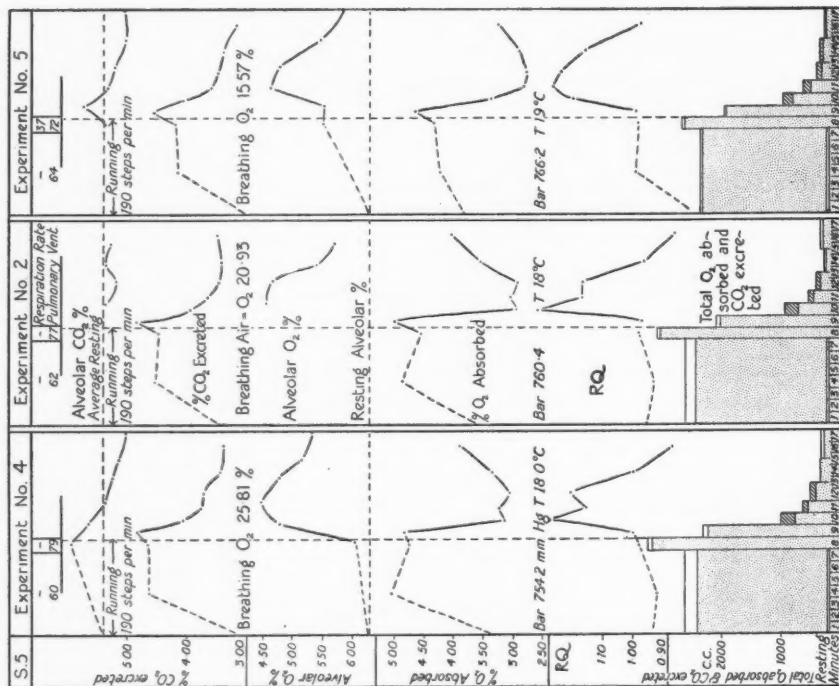


Fig. 21. Subject No. 5. The respiratory exchange during and after running at 190 steps per minute, breathing 26% O_2 , air (21% O_2), and 16% O_2 .

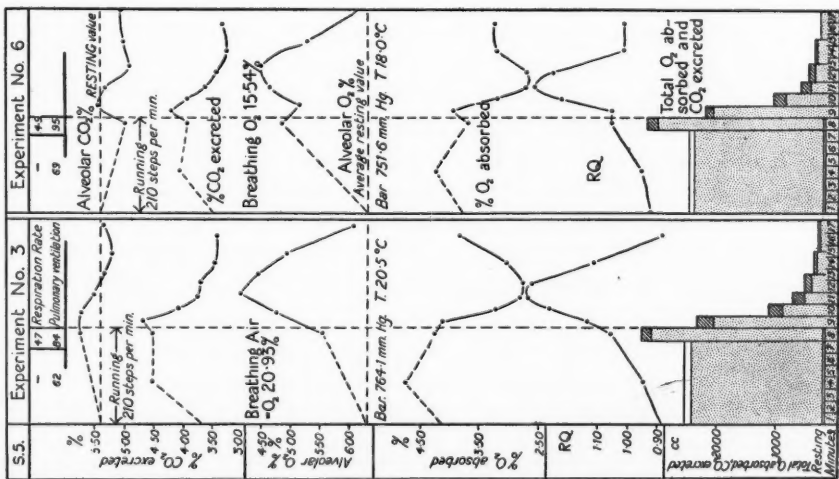


FIG. 22. Subject No. 5. The respiratory exchange during, and after running at 210 steps per minute, breathing air (21% O_2), and 16% O_2 .

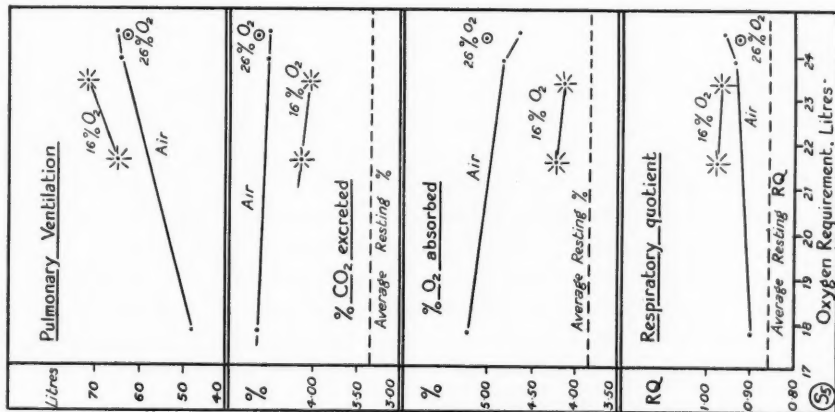


FIG. 23. Subject No. 5. 'Totals' calculated for the whole work period in all experiments, plotted against O_2 requirement.

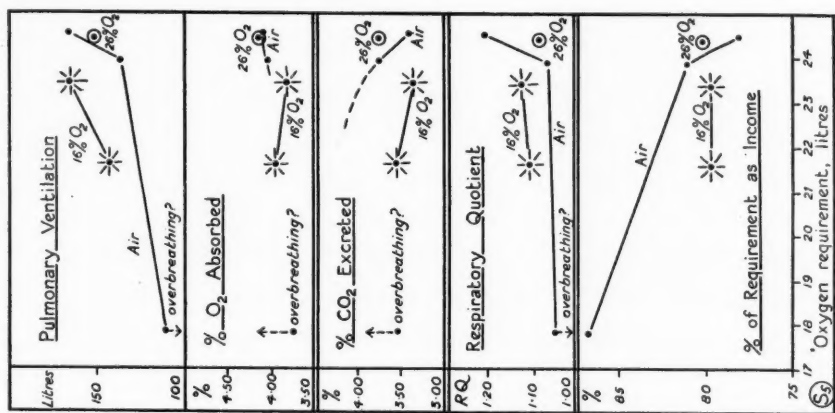


FIG. 24. Subject No. 5. 'Totals' calculated for the first 6½ minutes of recovery in all experiments, plotted against oxygen requirement. Lowest diagram partition of O_2 requirement between income and debt (30 minutes).

Experiments in air dots, 26% O_2 circles, 16% O_2 stars (see p. 395).



OBSERVATIONS ON THE SERUM CALCIUM IN PULMONARY TUBERCULOSIS AND ON TREATMENT BY INTRAVENOUS INJECTION OF CALCIUM¹

By WILLIAM BROCKBANK

(From the Pathological Laboratories of the Hospital for Consumption and Diseases of the Chest, Brompton)

Introduction.

THE work on which this paper is based was done whilst I was House Physician to Dr. Wall and Dr. Davidson at the Hospital for Consumption and Diseases of the Chest, Brompton.

I would like at the outset to thank these physicians for allowing me to use their cases and for the valuable criticism they made from time to time.

The work was suggested after studying the skiagrams of the lungs of patients suffering from pulmonary tuberculosis. Some of these photographs showed the presence in the lungs of calcareous nodules, and it seemed to be only in those cases where the tuberculous process had been wholly, or in part, arrested that this deposit of lime salts took place. The idea arose in my mind that it might be interesting to find out whether or not there was any increase or decrease in the amount of calcium in the serum, in cases of pulmonary tuberculosis, compared with the normal amount, and whether the amount varied at all with the degree of activity of the disease. In addition to this there were several other facts which seemed to suggest an important connexion between the element and the disease.

Calcareous nodules are, of course, frequently seen in the post-mortem room, both in cases where pulmonary tuberculosis is known to have been present and, more frequently, where it was unknown and unsuspected. Moreover, in those cases where the pulmonary tuberculosis has proved to be fatal there is generally no sign whatever of calcareous nodules.

The relation between the element and the disease is all the more striking when it is emphasized that in no other lesion of the lung—except certain cases of pneumonokoniosis—does nature attempt to combat the disease by depositing calcium salts in, or around, the lesion.

This process of calcification of a tuberculous lesion is not confined to phthisis, but is met with in tuberculosis of the lymphatic glands (notably in the mesentery) and also in the region of a tuberculous lesion of a bone or joint.

¹ Received March 3, 1927.

Lastly, there was one other striking fact—namely, that pulmonary tuberculosis was almost unknown amongst workers in lime.

I believe this observation was first made by Fisac of Spain in 1909. He is quoted by Fishberg (1) as saying, 'All workers in lime and plaster of Paris were immune to tuberculosis despite the fact that they lived in squalid dwellings and were underfed'.

Tweddell (2) investigated this statement by obtaining a list of all manufacturers of lime and plaster of Paris in the north-eastern States of America, and writing to the managers, asking them for the number of cases of pulmonary tuberculosis that had occurred amongst their employees. In their replies they all stated that no cases of pulmonary tuberculosis had ever been noticed amongst their men, who were remarkably free from colds and coughs. Many of these reports had added value coming as they did from the physicians employed by the firms. Similar reports were obtained from firms in Canada.

Rénon (3) reported that in a limestone region in the valley of Yonne, where there had been lime-kilns for ten years, among 200 employees, almost all alcoholics, none had tuberculosis. The lime-kilns even brought about a diminution of tuberculosis amongst the residents in the neighbourhood.

Iszard (4) quotes many authorities (5) who have published figures showing that there was less susceptibility to pulmonary diseases amongst workers in chalk-dust as compared with other dusts.

Selkirk (6), as a result of personal investigations amongst lime-workers, found that they showed exceptional health. He suggested that the absorption of lime salts offsets the demineralization produced by tuberculosis, and put forward the suggestion that individuals predisposed to tuberculosis should work in cement and lime, and that a lime-works should be started as a tuberculosis cure.

Tweddell (7) suggested that the calcium content of the soil was important in helping to prevent the spread of tuberculosis, for in Colorado and Mexico, where the soil contains a relatively high percentage of calcium salts, he states that pulmonary tuberculosis is rare amongst the native white population.

It will be observed, therefore, that there appears to be a very important connexion between calcium salts and tuberculosis, almost suggesting the use of calcium as a specific for treating the disease.

Physiology and Pharmacology.

The greater proportion of lime taken either as food or as medicine unquestionably leaves the body, unabsorbed, in the stools, but a small quantity is absorbed slowly and with difficulty from the stomach and small intestine. This circulates in the blood and is excreted mainly through the epithelium of the large intestine; a small quantity, however, is excreted in the urine.

The calcium circulates in the blood in two forms, partly as the carbonate, and partly combined with protein. De Wesselow (8) states that the latter combination accounts for 30 to 40 per cent. of the serum calcium, and points out

that the combination is loose, since the calcium can be quantitatively precipitated from the serum on the addition of ammonium oxalate.

The absorption of calcium from the alimentary canal is so slow that it is impossible to detect anything but slight increases in the serum calcium after the ingestion of a calcium meal.

Denis and Minot (9) state that the result of a study of the effect of administering calcium salts by mouth to men indicates that it is impossible to increase the concentration of calcium in the plasma by the ingestion of calcium salts.

This observation is borne out by Halverson and Bergeim (10), Neurath (11), Katzenellenbogen (12), Clarke (13), and Meigs, Blatherwick, and Cary (14), who publish figures showing that the serum calcium is only very slightly affected (if at all) by variations of the calcium in the diet.

When large quantities of calcium are thrown into the blood-stream, as by intravenous injection, the calcium remains abnormally high for a short period only, the excess of calcium being placed temporarily in an unknown organ, from which it is gradually withdrawn and excreted after the first excess has been eliminated (15).

Method.

The method chosen for the estimation of the serum calcium was that described by Kramer and Tisdall (16), and subsequently modified by Tisdall (17). It is fully described by Beaumont and Dodds (18).

All through the experiments duplicate determinations almost invariably agreed within 2 or 3 per cent. Variations of 5 per cent. in the serum calcium content (half a milligram per 100 c.c.) were not considered sufficient to warrant a repetition of the estimation, but on the rare occasions when the variation exceeded 5 per cent. the estimation was repeated. The margin of error is on the average 0.3 mg. per 100 c.c. serum. Precautions were taken in order to make sure that all apparatus and reagents were calcium-free. The syringes and needles were sterilized by immersion in spirit, and immediately before use were washed out with boiled distilled water. All reagents were quantitatively examined for calcium periodically, and the technique was rigidly adhered to.

Normal Serum Calcium.

It was considered advisable to begin these investigations with a series of estimations of serum calcium in apparently normal and healthy subjects, so that a standard figure should be obtained with which to compare the other results. Twelve such estimates were made, with the following results:

Case.	Sex.	Age.	Serum Calcium. mg. per 100 c.c.
A	Female	25	10.2
B	Female	25	10.1
C	Male	30	10.1
D	Male	16	10.5
E	Male	26	10.0
F	Male	40	10.3
G	Female	45	10.2
H	Female	50	9.8
I	Male	30	9.9
J	Female	16	10.1
K	Male	25	10.0
L	Male	26	10.3

The average value of these cases is 10.1 mg. calcium per 100 c.c. serum, the maximum being 10.5 mg. and the minimum 9.8 mg.

Various observers have given varying figures for the normal serum calcium value; and not only their mean figures but also their own individual figures differ very greatly, so that it is difficult to avoid the conclusion that there is something faulty in their technique.

The following table gives the normal values for the serum calcium as found by different observers:

Name.	No. of Cases.	Average.	Max.	Min.
mg. per 100 c.c.				
Jansen (19)	—	12.46	—	—
Dannstedt and Rumpf (19)	—	11.6	—	—
Hawk (20)	—	10	—	—
Myers (21)	—	10	—	—
Kramer and Howland (22)	7	9.6	9.9	9.3
Salvesen and Linder (23)	—	10	—	—
Matz (19)	50	10.28	12.0	9.0
Kramer and Tisdall (24)	10	10	10.5	9.5
Schamberg and Brown (25)	5	—	11.3	9.7
Percival and Stewart (26)	8	9.6	9.9	9.4
Kylin and Myhrman (27)	—	—	12.0	10.6
Vines (28)	8	10.7	10.76	10.2
Watchorn (29)	8	—	10.8	10.0

Comparison of these figures is extremely difficult, so wide is their divergence, but it illustrates the importance of the estimation by each worker of a series of serum calcium values on normal subjects.

Examination of Results.

Having obtained a series of values on normal subjects, the serum calcium was estimated in seventy patients suffering from pulmonary tuberculosis, some of them on two separate occasions. It was rather surprising to find that the difference between the values was negligible, although some weeks had elapsed between the first and second estimation.

Case No.	1st Estimation. mg.	Intervening Time. months.	2nd Estimation. mg.
14	9.8	4	9.6
23	10.2	2	10.0
39	9.0	2½	9.4
40	9.2	1	9.3
53	9.0	3	9.3
56	9.1	3	9.4
4	10.6	3	10.8
3	9.0	1	9.2

It will be observed that the widest variation is only 0.4 mg. per 100 c.c. (4 per cent.).

Age and sex seem to have no bearing on the values, so that the results will be considered in the first place under the headings of:

1. Active cases.
2. Arrested cases; together with a small third group—
3. Quiescent.

It is not always easy to divide cases in this way, as there are no symptoms characteristic of any of the groups, and not only the clinical findings have to be considered but also the whole history and course of the case, together with the bacteriological and radiological data.

Active Cases. In the bulk of active cases the tubercle bacilli are present in the sputum, and there are definite constitutional symptoms, such as pyrexia and tachycardia, in addition to the phthisical symptoms of cough, expectoration, pain, haemoptysis, emaciation, dyspnoea, and gastro-intestinal disturbance.

Pyrexia is present at some part of the day in nearly all the cases of active disease, but its absence does not necessarily exclude the condition. Any temperature not above 98.6° F. is regarded as normal.

Tachycardia also is another sign of activity—any pulse-rate over 80 being regarded as pathological.

Arrested Cases. The arrested cases are those in which the history, the physical signs, and radiological examination suggest an old tuberculous lesion, but in which the sputum is negative and there are no constitutional symptoms.

Quiescent Cases are those in which the lesion has not quite healed, the constitutional symptoms are very slight, and tubercle bacilli either absent from the sputum or found with difficulty.

If the cases are now examined under these headings the following tables are obtained:

Table of Active Cases.

(Pulse + means above 80: Temp. + means above 98.6° F.)

Case.	Sputum.	Pulse.	Temp.	General Condition.	Complications.	Calcium.
1	+	+	0	Good	Dysentery	10.1
2	+	+	+	Bad	—	8.6
3	+	+	+	Bad	—	9.2
4	+	+	+	Fair	—	{ 10.6 10.8

Table of Active Cases (continued).

Case.	Sputum.	Pulse.	Temp.	General Condition.	Complications.	Calcium.
5	+	+	0	Poor	—	8.6
7	+	+	0	Good	—	10.4
8	None	+	+	Poor	—	8.8
11	+	+	+	Poor	—	9.6
12	+	+	+	Bad	{ T.B. Larynx Mitral stenosis	10.0
13	+	+	+	Good		9.6
14	+	+	+	Poor	—	{ 9.8 9.6
17	+	+	+	Bad	—	9.0
18	+	+	+	Poor	—	9.6
19	+	+	+	Poor	—	9.2
22	None	+	+	Good	T.B. Larynx	9.0
23	+	+	+	Good	T.B. Larynx	{ 10.0 10.2
26	+	+	+	Poor	—	9.2
27	+	0	0	Poor	—	9.4
28	+	+	+	Fair	T.B. Larynx	9.6
29	+	+	+	Good		9.4
30	None	+	+	Fair	—	9.6
31	+	+	+	Poor	—	9.2
33	+	+	+	Poor	—	9.3
36	+	+	+	Fair	—	9.8
37	+	+	+	Bad	—	8.8
38	+	+	+	Good	—	8.6
39	+	+	+	Poor	—	{ 9.0 9.4
40	+	+	+	Good	—	{ 9.2 9.3
41	+	0	0	Fair	—	8.6
42	+	+	+	Poor	—	9.1
44	+	+	+	Bad	—	9.2
46	+	+	+	Fair	T.B. Larynx	9.8
47	None	+	+	Bad		9.2
48	+	+	+	Good	—	9.6
50	—	+	0	Good	—	10.6
52	+	+	+	Fair	—	11.0
53	+	+	+	Bad	—	{ 9.0 9.3
54	+	0	0	Good	—	9.6
55	+	0	0	Fair	—	10.9
56	+	+	+	Fair	—	{ 9.1 9.4
57	+	+	+	Fair	—	9.2
58	+	+	+	Poor	T.B. Tongue	9.2
59	+	+	+	Bad		8.8
60	+	0	0	Good	—	10.0
61	+	+	+	Bad	—	9.0
62	+	+	+	Fair	—	9.0
63	+	+	+	Fair	—	9.2
64	+	+	+	Poor	—	9.0
65	+	+	+	Fair	T.B. Larynx	10.0
66	+	+	+	Bad		9.0
68	+	+	+	Fair	—	10.2
69	+	+	+	Fair	—	9.4
70	+	+	+	Good	—	9.0

In these fifty-three cases the highest result is 11.0 and the lowest 8.6, the average being 9.4.

Arrested Cases. Turning to those cases classified as arrested, the following figures are obtained. All the cases had negative sputa and there were no constitutional symptoms.

Case No.	Serum Calcium. mg. per 100 c.c.
6	12.0
9	11.6
10	9.4
15	11.0
16	11.4
20	10.0
25	11.2
32	11.2
34	10.8
35	10.4
45	10.9
49	10.8
51	11.2

These thirteen cases have serum calcium values varying from 9.4 to 12.0, the average value being 10.9 mg. per 100 c.c.

Quiescent Cases. Lastly, there are four cases classified as quiescent.

Case 21 had a negative sputum—temperature rising to 99.2° for a few days—normal pulse-rate and good general condition. The serum calcium was 10.8.

Case 67 had a sputum in which an odd tubercle bacillus was found at the third examination. There were no constitutional symptoms. The serum calcium was 9.3 mg. per 100 c.c. serum.

Case 24 had a sputum containing very few tubercle bacilli. There were no constitutional symptoms. The serum calcium was 11.4.

Type of Case.	Total No. of Cases.	Max. mg.	Min.	Serum Calcium Average. mg.
Normal	12	10.5	9.8	10.1
Active Cases	53	11.0	8.6	9.4
Arrested Cases	13	12.0	9.4	10.9

In the above table it is observed that whilst the difference between the value of the serum calcium in normal and tuberculous subjects is not much, yet it is found that the value tends to be subnormal in active cases and rather above in arrested cases. Further subdivision of the cases was next made, using the classification of pulmonary tuberculosis suggested by Fishberg (30).

This classification, besides indicating the pathological condition, also indicates the prognosis, and consequently is much more satisfactory than other classifications.

Fishberg distinguishes at once between the acute and the chronic cases, and then subdivides the chronic cases, pointing out that

‘The ultimate outcome of the disease depends mainly on the relative intensity of the two processes in the lungs, the destructive and the reparative—the former manifesting itself by caseation and softening, and the latter by the formation of fibrous tissue which limits the destructive process and heals the lesion by cicatrization. Both processes of fibrosis and necrosis are caused by the tubercle bacilli. And, inasmuch as there are many cases in which fibrosis dominates the anatomical changes in the lungs and the symptoms thus produced differ from those in which the caseating process predominates, it is clear that there is justification for separation of fibroid phthisis into a distinct class of the disease. This justification is fortified by the fact that the prognosis of fibroid phthisis is distinctly more favourable than that of chronic caseous phthisis.

'In common chronic phthisis we find among the cases which have been described as "incipient" that there are many which show a marked tendency to cicatrization of the lesion, spontaneously or after some treatment for a few months. In the vast majority of cases this form of phthisis is not recognized, and only at the autopsy some scars or calcified foci are found in the lung or pleura, showing that the person had survived a tuberculous lesion. To treat these cases as we treat common chronic phthisis is wrong, and we have therefore described abortive tuberculosis as a distinct clinical type of the disease. Most of the victims of tuberculosis who succumb to the disease or who suffer from it for long periods of time, even if they recover, are affected with chronic phthisis. We have divided this subject into two parts—incipient phthisis and advanced phthisis.

'Finally, it is now known that phthisis occurs in the aged just as frequently as in younger individuals, but that it is not recognized very often because of the peculiar symptomatology it presents. Aged consumptives, believing that they only suffer from chronic bronchitis, asthma, or emphysema, are sources of infection not so fully appreciated as they deserve.'

Fishberg therefore classifies phthisis as follows :

1. Chronic pulmonary tuberculosis, incipient stage.
2. Chronic pulmonary tuberculosis, advanced stage.
3. Abortive pulmonary tuberculosis.
4. Fibroid type of pulmonary tuberculosis.
5. Acute forms of pulmonary tuberculosis.
6. Pulmonary tuberculosis in children.
7. Senile type of pulmonary tuberculosis.

I now propose to examine the *serum calcium values*, dividing the cases under the above headings.

Group I. Chronic pulmonary tuberculosis, incipient stage. In amplifying his remarks (already quoted) on this stage of his classification Fishberg describes in more detail the signs and symptoms of incipient pulmonary tuberculosis.

He gives as the main symptoms, cough, languor, anorexia, emaciation, pyrexia (which may be slight (99.4°), or which may occasionally rise to 101°, in which case there is little or no prostration), tachycardia, haemoptysis, and, occasionally, hoarseness due to early infiltration of the larynx. The physical signs may be defective resonance, with feeble, granular, cog-wheel or bronchial breathing together with râles or crepitations. Tubercle bacilli are generally found in the sputum.

The following cases in the series come in this group :

Case No.	Serum Calcium. mg. per 100 c.c.
1	10.1
4	10.7
13	9.8
24	11.4
29	9.4
41	8.6
45	10.9
54	9.6

In these eight cases the highest result is 11.4 and the lowest is 8.6, the average being 10.1 mg. of calcium per 100 c.c.

Group II. Chronic pulmonary tuberculosis, advanced stage. Of this stage Fishberg points out that all the symptoms enumerated under Group I are present in a more marked degree. The temperature is higher, the cough more annoying, and emaciation often very pronounced.

Physical examination shows extensive areas of diminished resonance together with displacement of the heart to the side affected, and there are signs of consolidation, softening, and cavitation.

The following cases seem to come under this group of the classification :

Case No.	Serum Calcium. mg. per 100 c.c.	Case No.	Serum Calcium. mg. per 100 c.c.
3	9.2	39	9.2
5	8.6	40	9.2
8	8.8	42	9.1
12	10.0	44	9.2
14	9.7	46	9.8
17	9.0	47	9.2
19	9.2	52	11.0
22	9.0	53	9.2
23	10.1	56	9.2
26	9.2	57	9.2
28	9.6	58	9.2
30	9.6	62	9.0
31	9.2	63	9.2
33	9.3	64	9.0
36	9.8	66	9.0
37	8.8	68	10.2
38	8.6	69	9.4

In these thirty-four cases the highest result is 11.0 and the lowest 8.6, the average being 9.3 mg. per 100 c.c.

Group III. Abortive pulmonary tuberculosis. The symptoms and signs of abortive tuberculosis are the same as those of incipient pulmonary tuberculosis, but they never pass beyond that stage. This class comprises patients in whom the disease, instead of pursuing the usual clinical course, is aborted within a few weeks or months of indisposition. It includes, of course, all those cases in which evidence of pulmonary tuberculosis has been revealed at an autopsy, although it was never suspected during life.

The following cases in the series belong to this group :

Case No.	Serum Calcium. mg. per 100 c.c.	Case No.	Serum Calcium. mg. per 100 c.c.
6	12.0	34	10.8
7	10.4	35	10.4
9	11.6	43	10.8
10	9.4	48	9.6
15	11.0	49	10.8
16	11.4	50	10.6
20	10.0	51	11.2
21	10.8	60	10.0
25	11.2	67	9.3
32	11.2	70	9.0

In these twenty cases the highest result is 12.0 and the lowest 9.0, the average result being 10.6 mg. per 100 c.c. serum.

Group IV. Chronic pulmonary tuberculosis, fibroid type. Clinically, this form of tuberculosis is characterized by an exceedingly chronic course extending over many years, finally leading, in most cases, to the development of the symptoms and course of the chronic form of pulmonary tuberculosis. It is mainly encountered in persons between 40 and 60 years of age. There are two varieties, the emphysematous form and the simple form.

The following cases come under these groups, but it was not considered worth while to separate them :

Case No.	Serum Calcium. mg. per 100 c.c.
11	9.6
27	9.4
55	10.9
65	10.0

In these four cases the highest result is 10.9 and the lowest 9.4, the average being 10.0 mg. per 100 c.c. serum.

Group V. Acute pulmonary tuberculosis. Fishberg defines acute pulmonary tuberculosis as an active, chronic phthisis without the remissions and ameliorations characteristic of the course of the latter affection, and he describes two types, acute pneumonic tuberculosis and acute miliary tuberculosis.

The following cases in the series belong to this group :

Case No.	Serum Calcium. mg. per 100 c.c.
2	8.6
3 (on admission)	9.0
59	8.8
61	9.0

In these four cases the highest result is 9.0 and the lowest 8.6, the average being 8.85 mg. per 100 c.c. serum.

Group VI. Pulmonary tuberculosis in children. No cases.

Group VII. Chronic pulmonary tuberculosis, senile type. Here the physical signs and symptoms are those met with in adults in general, but the disease, which in all probability was acquired in infancy and had been held in abeyance throughout life, had only broken out again at the period of life when the organs of the body began to suffer as a result of wear and tear.

Only one case from the series comes in this group, No. 18; the serum calcium value being 9.6 mg. per 100 c.c.

Comparison of Results.

Let me now tabulate these results, arranging the groups in their order of severity, beginning with the acute type :

Group.	No. of Cases.	Serum Calcium.		
		Max.	Min.	Aver.
Acute	4	9.0	8.6	8.85
Chronic (advanced)	34	11.0	8.6	9.3
Senile	1	—	—	9.6
Fibroid	4	10.9	9.4	10.0
Chronic (incipient)	8	11.4	8.6	10.1
Abortive	20	12.0	9.0	10.6

These results bear out the observations made in the first collective examination. They are much more valuable, however, because they are classified in a more accurate manner—a manner which suggests a prognosis.

The acute and the chronic advanced cases have a bad prognosis, and it is interesting to note that the serum calcium is distinctly lower than in the chronic incipient and abortive cases in which the prognosis is favourable.

Treatment of Haemoptysis by Calcium.

Amongst the various drugs used to combat haemoptysis is calcium, which has been given in various ways on the assumption that the serum calcium was low and that an increase would assist coagulation. In the following series the patients had haemoptysis whilst in hospital, and the estimations were made during the attacks; in four cases results were also obtained when the patient was free of the symptom.

Case No.	Amount of Blood.	Serum Calcium. mg. per 100 c.c.
3	Rusty sputum	9.1
22	3 oz. several times	9.0
26	3 oz. several times	9.2
30	Coloured sputum	9.6
31	Coloured sputum	9.2
39	6 oz.: coloured sputum, 2 weeks	9.2
40	Coloured sputum	9.2
42	14 oz.: coloured sputum, many days	9.1
53	Coloured sputum	9.2
66	Coloured sputum	9.0

The average serum calcium figure works out at 9.2, and this has to be compared with that for the chronic advanced cases, to which group each of these cases belonged. The serum calcium value for this group was 9.3. There is, therefore, only a trifling difference between the figures, and this is borne out when the following cases in which the serum calcium values were estimated on different days are considered.

In two of these cases the first estimation had been made some time before the patient had the attack of haemoptysis; whilst in the other two cases the preliminary estimation was made during the attack.

Case No.	Before Haemoptysis.	During. mg. per 100 c.c.	After.
3	—	9.0	9.2
39	—	9.0	9.4
40	9.2	9.3	—
53	9.2	9.3	—

It will be observed that the variations are negligible, and that whereas in two cases the value during the attack was slightly higher, in the other two cases it was a trifle lower as compared with the results determined at a period when the patient was not coughing up blood.

Summary.

1. The serum calcium values are, on the average, slightly lower in cases of advanced pulmonary tuberculosis than they are in normal subjects.
2. The serum calcium values are, on the average, slightly higher than normal in cases of pulmonary tuberculosis which have healed or are healing.
3. The average values appear to decrease inversely with the severity of the disease, there being a 20 per cent. difference between the highest and lowest averages.
4. Stress must be laid on the fact that it is only average values that are being dealt with. Individual variations in the groups are sometimes rather marked, and thus it does not seem that a trustworthy guide to the activity of the disease can be found by estimating the serum calcium content.
5. The serum calcium values seem to be rather steady in each individual; any alteration in the value must be very gradual.
6. Haemoptysis does not appear to affect the serum calcium values in any way.

Work by other observers.

After an extensive search I can only find one paper which contained the results of experiments similar to those recorded in this paper. They were performed by Matz (19), and his figures are:

	Serum Calcium. mg. per 100 c.c.
Chronic phthisis apparently arrested (6 cases)	10.78
Incipient phthisis (10 cases)	10.38
Chronic phthisis with moderate amount of lung involvement—clinical activity not pronounced (20 cases)	10.0
Chronic phthisis with tuberculosis of kidney (1 case)	9.7
Chronic phthisis with small amount of lung involvement and history of haemorrhage (1 case)	9.4
Chronic phthisis, advanced, with large lung involvement and history of haemorrhage (9 cases)	9.25
Chronic phthisis, advanced, with large lung involvement and with no history of haemorrhage (20 cases)	9.25
Chronic phthisis with chronic parenchymatous nephritis (4 cases)	9.22

These figures are very similar to mine, and they, too, show that the serum calcium in pulmonary tuberculosis is highest when the disease is arrested. They also show that haemoptysis does not appear to affect the serum calcium values.

Other workers have investigated the serum calcium values in other diseases. It seems to be agreed by observers that in nephritis of all kinds the values are diminished, 7.3-11 (31). In tetany the values range between 3.7 and 7.5 (32), whilst in cases of fibrositis the serum calcium is increased to between 12.1 and 12.7 (33).

Thus, it is not only in phthisis that the serum calcium is decreased.

OBSERVATIONS ON THE EFFECT OF RAISING SERUM CALCIUM IN ACTIVE PULMONARY TUBERCULOSIS.

Early in these investigations, when it was observed that the serum calcium was lower than normal in active cases of phthisis, and rather higher than normal in healed cases, I wondered what the effect of raising the serum calcium in a patient suffering from active pulmonary tuberculosis would be.

The first problem was to decide on the method of administering the calcium. Various writers state that oral administration of calcium does not materially affect the serum calcium, and this observation was confirmed by administering 15 grains of calcium lactate orally three times a day to six different patients over a period of a fortnight. The serum calcium was in each case estimated before the experiment, after seven days, and after fourteen days, the blood in the latter two instances being taken four hours after a dose of calcium lactate.

Case No.	Before.	After 7 Days. mg. per 100 c.c.	After 14 Days.
1	10.0	10.2	10.1
2	9.3	9.3	9.3
3	11.1	11.0	10.9
4	9.8	9.5	9.9
5	9.6	9.8	10.1
6	8.8	9.0	9.0

On the strength of these results it was decided to give the calcium intravenously. The salt used was calcium chloride made up with distilled water to the strength of one grain in 100 minims and sterilized.

I administered $1\frac{1}{2}$ grains of calcium chloride every other day and found that the serum calcium twenty-four hours after an injection was raised to between 12 and 13 mg. per 100 c.c., but that it had generally fallen to between 10 and 11 mg. forty-eight hours after injection. As the injections were given every other day the serum calcium was kept rather above the normal during the whole course of the treatment.

Calcium chloride, if given hypodermically, is apt to produce gangrene at the site of injection, and therefore great care was necessary to make sure that all of the solution was injected into the vein.

The injections seemed to have no ill effects on the patients, though they complained of a sensation of heat all over the body as the solution was being injected. The following are the case notes of the six patients concerned. The small number of cases was due to the fact that very few patients remained in hospital as long as four weeks, and of those who remained longer it was considered advisable to pick only the cases that were not making satisfactory progress on the ordinary methods of treatment.

Case A. (No. 37 of the Series.) Male, aged 32, single. Occupation, metal carter; was admitted to hospital on January 27, 1926, complaining of a slight cough, which had troubled him for the previous two months, but had been much worse during the fortnight preceding his admission. He was very emaciated and short of breath. Sputum positive 29.1.26. He was pale, thin, and ill and on admission was found to have advanced pulmonary tuberculosis. There was infiltration of all three lobes of the right lung and also of the upper lobe of the left lung, with signs of cavitation and softening of the right upper lobe.

Weight on admission 9 stone 12 lb. Temperature 99-102°. Pulse 96-120.

22.3.26. Two months after admission. Much weaker—physical signs rather more extensive. Temperature 98-101°. Pulse 96-120. Weight 9 stone 0 lb. Regarded as a hopeless case.

23.3.26. Calcium chloride injections commenced, gr. 1½ intravenously three times a week.

12.4.26. Much better—evening temperature normal. Pulse 88-112.

3.5.26. Temperature 97-98.4°. Pulse 88-96. Weight 9 stone 4 lb.—patient getting up two hours a day.

19.6.26. Injections discontinued. Temperature had been normal (with odd exceptions) for nine weeks. Pulse 80-100. Weight 9 stone 9 lb.—patient up six hours.

23.7.26. Patient transferred to Eversfield Sanatorium. He was greatly improved, though still rather anaemic. Temperature subnormal. Pulse 80-96. Weight 10 stone 3 lb. Physical signs were much as before, but moist sounds could only be heard occasionally. Sputum practically nil and tubercle bacilli only found with difficulty.

Progress Notes. I am informed that he progressed very satisfactorily for two months, having a subnormal temperature. He then caught a cold and developed a patch of dry pleurisy on the right side. The temperature soon settled to normal, but unfortunately the patient discharged himself on October 14. He had gained 5 lb. whilst at the Sanatorium.

Case B. (No. 68 of the Series.) Male, aged 25. Occupation, baker's assistant; was admitted into hospital on January 4, 1926, complaining of a persistent cough following a febrile attack in the previous July. His general condition was fair, but his evening temperature often exceeded 99°. He was sickly and seemed to make no progress.

Pulse 80-104. Sputum positive.

The physical signs indicated that there was consolidation and softening of the left upper lobe of the lung, with infiltration of the right upper and left lower lobes.

On March 23 (2½ months after admission) the intravenous injections were commenced, and although it was a few weeks before the evening pyrexia ceased his general condition improved noticeably and the biliousness disappeared. He was able to get up and began to put on weight. His complexion, which had been rather 'muddy', became very healthy, so much so that the Sister laughingly suggested giving the injections as a 'beauty treatment'. He was, however,

rather liable to pyrexial attacks, in which the temperature would shoot up to 100–101° after the manner of an influenzal attack, settling down in a few days.

The injections were discontinued on July 3, but he had another spell of pyrexia lasting rather longer than usual. The injections were therefore recommenced on August 3, but in the meantime the patient had put on 22 lb. weight. His sputum was re-examined on May 6, and only a few tubercle bacilli were seen. After that date the sputum dried up.

Progress Notes. I am informed that following the recommencement of the calcium injections this patient soon began to improve. The temperature settled in a fortnight and he began to get up again. Improvement was maintained, and when he was transferred to Frimley Sanatorium on September 14 the temperature had settled completely and he had gained a further 12 lb. since the recommencement of the injections six weeks previously.

Case C. (No. 12 of the Series.) Male, aged 19. Labourer; was admitted to hospital (as an urgent case) on March 18, 1926, complaining of cough and huskiness, and although he was not apparently short of breath he was rather cyanotic. He had had rheumatic fever in 1923 and pleurisy six months before admission. He was tall, thin, pale, and cyanosed. His heart was enlarged and there was a presystolic murmur. The sputum was positive, and there was evidence of infiltration of the right and left upper and lower lobes of the lungs.

Intravenous injections of calcium chloride were commenced on April 23, and were continued until June 7, when he was transferred to a Poor Law Infirmary. In this case the injections seemed to have no beneficial effect.

Case D. (No. 3 of the Series.) Male, aged 33. Occupation, railway policeman; was admitted into hospital on April 12, 1926, in a very grave state. Eight days previously he had a sudden onset of fever with pain in the right chest and cough, and had been treated as a case of pneumonia. He was delirious for two days. The temperature fell by lysis on the 13th and 14th days of the illness and remained subnormal for three days, but the pulse had remained frequent and the respirations 28. On April 23 (the 19th day) the evening temperature was 101°. It remained high and on the 26th became inverse. The temperature remained inverse (with the exception of one day) until May 26. The fever gradually became more marked and the condition was becoming very serious again when, on May 15, tubercle bacilli were found in the sputum after they had been reported absent twenty-one times. (They were also reported present a few days later.)

At this time there was evidence of infiltration of all the lobes of the right lung and also of the upper lobe of the left lung, with signs suggesting cavitation at the right base.

Injections were commenced on May 21, five weeks after admission—the temperature then being 102–99° and the pulse 120–100. Five days later the temperature was much lower and next day had changed to the normal swing. After ten days it had fallen to 99·6°, and in another week to normal; pulse 84–100. The patient made uninterrupted progress and the injections were stopped on June 30; and when he was transferred to Ventnor on July 15 he looked the picture of health, having put on 22 lb. weight since the injections commenced. For the last four weeks there had not been any sputum.

Progress Notes. He remained in Ventnor until September 9, leaving for business reasons. During the whole of this time his temperature never rose above the normal and his pulse on discharge was 72. He gained another 20 lb., making a total gain of 3 stones since the injections commenced 3½ months previously.

Tubercle bacilli were found in the sputum on one occasion—the last three reports, however, were negative.

Case E. (No. 64 of the Series.) Female, aged 18. Occupation, clerk; was admitted to hospital on April 9, giving a history of cough and progressive emaciation over a period of twelve months. She was anaemic and poorly. The sputum was positive and there were signs of cavitation and fibrosis of both lobes of the left lung. Her temperature varied between normal and 101° , and her pulse was 88-124. She had made such poor progress at the end of three weeks that it was decided to commence a course of calcium injections on May 1. The evening temperature gradually fell to $98.4-99^{\circ}$ and she began to put on weight.

On June 12 it was decided to stop the injections on account of the difficulty of getting into the veins. The evening temperature remained about 98.6° until July 17, when she developed symptoms of bronchitis. The temperature remained up for two weeks and then gradually fell. Since the injections had commenced the patient had put on 18 lb. weight and her general condition showed a marked improvement.

Progress Notes. I am informed that the temperature rapidly settled and became normal, and on October 4 she was transferred to Frimley Sanatorium, having a subnormal temperature and a pulse-rate of 80, despite the fact that she was allowed up all day. In this period she had gained 4 lb. weight.

Case F. (No. 57 of the Series.) Female, aged 33. Occupation, matron; was admitted into hospital on April 12, 1926, complaining of cough and pain in the right chest following pneumonia in January. Her general condition was poor, and the physical signs indicated that there was cavitation and fibrosis in each of the lobes of the right lung. The temperature varied between 98° and 101° and the pulse between 90 and 120. Despite the fact that there were signs of pleurisy an artificial pneumothorax was induced on May 20. The refills were only small, very little collapse of the lung took place, and the temperature, instead of settling, became rather more irregular; pulse 106-124.

The refills of the pneumothorax were discontinued on July 9 and injections of calcium chloride commenced, and on August 3 the temperature appeared to be settling, although there was little or no improvement in her appearance.

Progress Notes (Nov. 1926). The injections were still being given to the patient. I am told that 'with occasional interludes she seems to improve gradually'.

Discussion.

Naturally it is not wise to attempt to draw any definite conclusions from six cases, but those of us who watched them from day to day felt that the results were encouraging. We realized of course that the treatment was in no way a specific treatment, for in not one of the cases did the sputum rapidly change from positive to negative.

Cases A, B, D, and E showed a much greater improvement than had ever been thought possible, and in the cases of A and D the improvement was maintained after the injections had been discontinued. Case B had a relapse shortly after the cessation of the treatment, but on its recommencement he rapidly regained the ground he had lost. Case E also had a relapse which seemed to be an attack of simple bronchitis, and the temperature soon settled and became subnormal.

Regarding these four cases the most striking features were:

1. The gradual fall of temperature to normal. All cases had failed to respond to treatment by 'absolute rest'.

2. The progressive gain in weight. Following the commencement of the injections the patients put on weight as under :

A.	Male	22 lb. in 7 months.
B.	Male	34 lb. in 6 months.
D.	Male	42 lb. in 3½ months.
E.	Female	22 lb. in 5 months.

3. The alteration of the complexion from one of pallor to one of a much more healthy hue.

Case F. Is improving gradually under the treatment.

Case C. Must be looked upon as a failure, but although he did not improve, he was none the worse for the injections.

Much more work must be done on the subject before the value of the treatment can be estimated, and further investigations are necessary to determine the best method of administration of the calcium.

It has been proved that there is little or no absorption of calcium salts administered orally, but some observers point out that calcium metabolism is increased somewhat by the administration of cod-liver oil. Again, it is claimed that parathyroid extract increases calcium metabolism, but whether either of these methods would give the results stated by the more direct method of administration used in this series of experiments I do not know.

Another point which requires attention is the question of the length of time that calcium administration is desirable. One case in the series suffered a definite relapse after the treatment had been discontinued, and it became necessary to repeat the injections.

Conclusions.

1. An attempt has been made to find out whether there are any changes in the amount of calcium in the serum in cases of pulmonary tuberculosis as compared with the amount in normal healthy persons.

2. Seventy cases of pulmonary tuberculosis have been examined and the serum calcium value has been found to vary between 8.6 and 12 mg. per 100 c.c., the normal value being 10 mg. per 100 c.c. serum.

3. When the cases were graded according to their severity it was observed that, on the average, the calcium was decreased in quantity in the serum when the disease was acute, and that it was increased when the disease had healed, with proportionate results in the intermediate stages. The difference amounted to 20 per cent.

4. Individual results, however, varied, and, for this reason, I do not think that the estimation of the serum calcium can be used as a trustworthy guide to the activity of the disease.

5. The serum calcium is not diminished in patients who are coughing up blood, as compared with patients in a similar stage of the disease, but without that symptom.

6. The results suggest that calcium may be beneficial if given to phthisical patients.

7. It was found that calcium, if given by mouth, failed to alter the serum calcium materially, but when given intravenously the serum calcium was raised above the normal for forty-eight hours.

Six patients received calcium intravenously with results so encouraging that I intend to continue this line of treatment on suitable cases which come under my care.

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MULTIPLE NODULAR HYPERPLASIA OF THE LIVER¹

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With Plates 8 and 9

BOTH acute atrophy of the liver and portal cirrhosis are well known. Cases of an intermediate character and representing all grades of transition between these two conditions are not so well known, but have been recorded in the literature by many observers. The liver responds in a different manner to toxins of varying intensity and duration. In acute yellow atrophy there is a marked and rapid destruction of liver cells, usually of patchy distribution. In those cases which terminate fatally in less than four days, the liver, *post mortem*, is shrunken and yellow, and there are no evidences of regeneration.

If the damage be less rapid and extensive, the disease becomes more prolonged, and warrants the name 'subacute atrophy'. Here, in addition to destructive changes, well-marked vascular and inflammatory reactions are present. There are large areas of young connective tissue containing inflammatory cells and new bile-ducts, and considerable proliferation of liver cells forming adenomatous nodules. Clinically, these cases are usually fatal in a few weeks. If the damage be not too extensive, it is probable that regeneration may take place to a sufficient extent to allow at least temporary or even, perhaps, permanent recovery.

In multiple nodular hyperplasia the liver has probably been subjected to repeated subacute attacks, each being accompanied by degeneration and followed by regeneration producing nodules simulating adenomata. Clinically, the course is usually prolonged and may last several months or one or two years. The first case of this kind was reported by Cayley (1) in 1883, under the name of subacute atrophy, and further cases have been recorded in recent years by Miller and Rutherford (2), McDonald and Milne (3), and others. In most cases the liver at death is small and nodular and shows macroscopically and microscopically the appearances about to be described in the two cases here reported. There is no sharp line of demarcation between this condition and portal cirrhosis, where toxins of lesser intensity from time to time cause damage to liver cells, accompanied by regeneration and fibrous tissue formation. Many cases of multiple nodular hyperplasia have probably been diagnosed as portal cirrhosis or adenoma,

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but in typical cases a diagnosis should be possible if the condition is borne in mind. Usually the first symptom complained of is jaundice, which is persistent but of variable intensity relative to repeated subacute attacks: the jaundice is much deeper and appears much earlier than in portal cirrhosis. There may be pain in the right hypochondrium, probably due to peri-hepatitis, but such pain in our experience is also not uncommon in cirrhosis of the liver, particularly in the syphilitic variety. There is usually a progressive deterioration in the patient's general condition, and towards the end ascites sometimes develops rapidly. The liver, which may have been palpable in the earlier stages, becomes progressively smaller, and later cannot be felt. The spleen is usually moderately enlarged. Tuberculosis, as in portal cirrhosis, is a common complication, but haematemesis rarely occurs. The clinical picture, therefore, is different from that seen in portal cirrhosis. Pathologically, although there are cases of an intermediate type, the differences between the two conditions are usually well marked. In multiple nodular hyperplasia the nodules are larger and smoother, there is more evidence of regeneration in bile-ducts and liver cells, and the connective tissue is more embryonic in type and contains more inflammatory cells.

Case Reports.

Case I. Female, aged 10 years, admitted to the Melbourne Hospital on February 10, 1926. Family and past history negative. Her illness began nine months before admission with an attack of jaundice lasting three weeks. At this time she was feverish and lost her appetite, the stools were pale and the urine dark in colour. A month later she had had a similar attack and had been more or less jaundiced ever since, her stools varying in colour with the intensity of the jaundice. During the last two months she had had occasional attacks of very severe pain in the right hypochondrium, and a few days later she developed thirst and polyuria. Throughout her illness there was loss of appetite, but she had never vomited. One month before admission the abdomen began to swell and had progressively increased in size.

On examination there was well-marked jaundice. Temp. 99° F., pulse 104, and respiration rate 24. General condition good. Heart, nothing abnormal. There was well-marked ascites and the veins in the lateral abdominal wall were very prominent. The spleen was palpable. The legs showed slight oedema. Urine sp. gr. 1002, no albumen or sugar, but both bile salts and bile pigments were detected. The Wassermann and hydatid tests were negative. There was mild secondary anaemia. The Fouchet test was positive, and the van den Bergh test gave a biphasic reaction. On February 11 the abdomen was tapped and five pints of straw-coloured fluid, sp. gr. 1010, removed. No tubercle bacilli were found, and a guinea-pig was injected with negative result. After tapping, the abdomen was again examined and the liver could not be palpated. The fluid rapidly reaccumulated. The jaundice definitely decreased during the patient's stay in hospital, but her general condition was gradually getting worse and the ascites steadily increased. On March 10 the abdomen was opened, the ascitic fluid removed, and an omentopexy performed. The patient did not rally after the operation, and died three days later.

At autopsy the liver was much reduced in size and weighed 20 ounces. The surface was pale, with congested blood-vessels here and there. The upper portion was very nodular and adherent to the diaphragm by dense, highly vascular adhesions. On section, the capsule was slightly thickened and two definite areas

could be distinguished. First, a large spherical mass about four inches (10 c.c.) in diameter, occupying most of the upper part of the right and left lobes, and sharply demarcated, though not by a capsule, from the remainder of the liver substance. This mass was composed of a large number of nodules, varying in diameter from two to four millimetres, and of a yellowish green colour. A few of the nodules showed necrosis in the centre. In between the nodules the tissue was firm and of a greyish red colour. The second area comprised the whole of the remainder of the liver, which was greyish red in colour and moderately firm. The portal canals were prominent, blood-vessels were numerous, and there was some bile stasis. The gall-bladder and ducts were normal.

On microscopic examination the nodules were composed of liver cells, but the lobular arrangement was markedly disturbed. In many places where the trabeculae were cut in transverse section a distinct lumen was visible. At the centres of many of the lobules the liver cells stained poorly and the nuclei showed degenerative changes. At the periphery of the lobules the liver cells showed evidences of regeneration: they varied markedly in size and the nuclei showed considerable variation in their structural appearance, some being small and deeply stained, and others large, vesicular, and with active chromatin network. Some of the cells possessed two nuclei, but no mitotic figures could be seen.

The tissue in between the nodules and forming the whole of the remainder of the liver substance was composed of recent granulation tissue. The cells in this tissue were closely packed, and many were quite plump and fibroblastic in type. There were many inflammatory cells, chiefly lymphocytes, which in places were aggregated to form small nodules. The vessels were numerous and thin-walled, and a few small haemorrhages were present. Numerous small bile-ducts, sometimes connecting with liver trabeculae at the margins of the lobules, could be seen, and the transition between the two types of cell was always quite abrupt. In some areas, where liver cells were completely absent, the central vein of the lobule still persisted, and at the margin 'new bile-ducts' were observed radiating in for a short distance from the periphery. These were easily distinguishable from old ducts, which were still visible in the portal canals, by their smaller size and deeper staining. Although careful search was made, nothing suggesting proliferation of liver cells from the extremities of bile ducts could be seen. The spleen was moderately enlarged and weighed 8 ounces. It was firm, and there was no peri-splenitis. Microscopically there was a marked decrease in the lymphocytes, both in the region of the Malpighian corpuscles and the pulp, and there was a considerable increase in the supporting framework.

Both kidneys, aggregate weight $6\frac{1}{2}$ ounces, were tough and showed extensive scarring. On section the cortex was with difficulty distinguished from the medulla and the whole surface was blurred and indistinct. Microscopically there was marked infiltration of the cortex and medulla with young connective tissue similar to that seen in the liver. There were also numerous lymphocytes and a few scattered lymphoid nodules. The heart was small, weight 4 ounces, but otherwise normal. Throughout both lungs there was much fine fibrosis and emphysema: there was no evidence anywhere of tubercle: microscopic examination showed fibrosis, and again the connective tissue was very rich in cells and infiltrated with lymphocytes. The pancreas was tough and microscopic examination showed infiltration of the gland with recent cellular connective tissue. The stomach showed many dilated blood-vessels beneath the mucosa, which in between was very pale and atrophic. The brain was examined, but no changes were found in the basal ganglia.

Case II. Male, aged 18 years, admitted to the Melbourne Hospital on July 7, 1926. Family and past history negative. For the past six months he had had jaundice of varying intensity, intermittent headache, and weakness and

lassitude. The urine had been dark and the stools clay-coloured. During the last month he became worse and had had two attacks of vomiting, but no pain. In the last two weeks he had been very short of breath, but had had no swelling of the legs or feet. His bowels had been regular, his appetite good, and he had had no urinary symptoms. Sixteen hours before admission he suddenly developed a right-sided hemiplegia with aphasia, but did not lose consciousness. He had vomited profusely at the onset of the hemiplegia, but not since.

On examination he was definitely jaundiced. Systolic pressure 150 and diastolic 50 m.m. The heart was slightly enlarged, and there were murmurs suggesting aortic and mitral disease. An examination of the lungs and abdomen revealed nothing abnormal. Pupils and fundi normal: there were physical signs of a right hemiplegia. Lumbar puncture was performed and 25 c.c. of blood-stained fluid, under increased pressure, removed. The fluid was cultured and no growth obtained. The Casoni reaction and the hydatid complement fixation test were negative. The Wassermann reaction in the blood was strongly positive, but on repeating the test a negative result was obtained. The Fouchet test was positive and the van den Bergh test gave a biphasic reaction. Four days after admission the patient began to run a temperature. His condition steadily became worse, and he became comatose and died on July 23, 1926.

Post mortem the liver weighed 48 ounces. The surface was very pale, in parts wrinkled, and bossed by nodules of varying size. On section there were numerous yellowish grey areas, varying in diameter from 1 m.m. to several centimetres and corresponding to the nodules on the surface. In between the yellow areas the liver tissue was firm and reddish grey in colour. There was no peri-hepatitis.

The aortic and mitral valves showed the vegetations of infective endocarditis. The lungs were congested throughout: the kidneys were large and pale but not infarcted. The spleen weighed 20 ounces, and at the upper and lower poles there was great hypertrophy of the Malpighian bodies. The pancreas was large, 8 ounces, and in places firm and the capsule thickened. In the left parietal lobe of the brain was a large haemorrhage extending from just beneath the cortex to the basal nuclei and lateral ventricle, into which the blood had ruptured. The other organs showed no changes worthy of note.

Microscopic examination of the liver showed that the nodules were composed of liver cells occurring singly or in small masses with occasional trabecular arrangement, and only here and there an attempt at lobular formation. In some areas the cells were pyramidal in shape, and as many as eight or ten could be seen arranged around a distinct lumen, presenting a marked resemblance to the appearance seen in sections of embryonic liver. The liver cells varied from about 10μ to 60μ in diameter, and many of them were multinucleate, the number of nuclei varying from one to ten. Most of the nuclei were large and vesicular, with active chromatin network, but a few were small and pyknotic. The absence of orderly arrangement into lobules and trabeculae, the presence of multinucleate cells, the grouping around lumina, the variation in the size of the cells, and the appearance of the nuclei all suggested rapid proliferation of liver cells. The tissue in between the nodules was very similar to that seen in Case I. It consisted chiefly of connective tissue of an embryonic type, containing numerous fibroblasts, lymphocytes, and a few plasma cells and endothelial cells. There were numerous new bile-ducts and a few isolated masses of liver cells. In a few cases new bile-ducts terminated in a small club-shaped mass of cells, resembling liver cells and suggesting that the latter had arisen by proliferation from the former.

With regard to aetiology, nothing definite has been determined. In the cases described in the literature there was no constant aetiological factor. Tuberculosis

was frequently present, but there was nothing to show that it was in any way causally related. Ueber (4), writing in 1920, considered syphilis an important factor, but out of ten cases cited only one was syphilitic. He also ascribes an important place to gastro-intestinal catarrh, but produces no definite evidence to support this. Fraser (5) produced a similar condition in rabbits by injection of diphtheria toxin. The disease is probably due to a toxin, but whether it be metabolic or microbic, or arising partly in the liver itself from liberation of its own ferments, we at present do not know.

In Case I there was nothing in the history or the post-mortem examination to suggest an aetiological factor. In Case II an ulcerative endocarditis was present, but, in view of the fact that the changes in the valves were recent, this was probably a terminal infection and not causally related to the liver condition. Both the liver disease and the endocarditis may have been due to some undiscovered focus of infection. In this case also the blood at first reacted to the Wassermann test, but on repeating the test a negative result was obtained. *Post mortem* there were no lesions characteristic of syphilis, and the presence of this disease cannot, therefore, be regarded as proven.

In the cases recorded in the literature there is very little reference to changes in other organs in the body with the exception of the spleen, which is usually enlarged, congested, and shows an increase in the reticulum with a decrease in lymphocytes. In view of this many authorities have assumed that the toxins causing the disease are carried by the portal blood. Miller and Rutherford state that as a rule the other organs show no characteristic changes. Verse (6) has described a case in which there was an associated interstitial pancreatitis, and another has been recorded with fibrotic changes in the kidney. In Case I there were marked pathological changes, not only in the liver and spleen, but also in the kidneys, lungs, and to a lesser extent in the pancreas. These changes were of too long standing to have been terminal, and were probably due to the same toxin as that causing the liver damage. In Case II, apart from the pathological changes due to the endocarditis, there were no important changes except in the liver and the spleen.

In studying the microscopic sections of the liver there were two features of outstanding interest, the marked evidences of regeneration of liver cells and the numerous so-called 'new bile-ducts'. Numerous observers have demonstrated the great powers of proliferation possessed by liver cells. Whipple (7) has shown that destruction of two-fifths of each lobule in the dog can be made good in a few weeks by regeneration. Ponfick's (8) experiments showed that after removal of a large part of the liver, the remainder enlarged by symmetrical growth of each lobule, new cells being formed by division of old ones. In man, many diseases associated with destruction of liver cells are followed by evidences of regeneration. The liver cells can divide by mitosis or by direct division. Most of them arise by division of pre-existing liver cells, but in Case II small masses of cells, resembling liver cells, could be seen at the extremities of some of the new bile-ducts, suggesting that the former had arisen by proliferation from the latter.

This, however, occurred so infrequently that it would seem to play a very minor part in the process of regeneration.

Ever since the so-called 'new bile-ducts' were first described by Wagner (9) in 1862 a great diversity of opinion has been expressed as to their origin and significance. It has now been established by numerous observers that they form a communication between liver trabeculae and interlobular bile-ducts. In serial sections Milne, MacCallum, and others have definitely proved this connexion, and in Case I this relationship could also be observed. It would seem, therefore, that the new bile-ducts must arise from liver cells or bile-ducts, either in consequence of atrophic or regenerative processes. Aschoff (10), Klebs (11), Rolleston (12), and Marchand (13) consider that they are atrophic liver cells. Ribber (14) and Schmidt (15) thought that they resulted from proliferation of liver cells. That they were simply due to destruction of liver cells and a resulting crowding together of interlobular bile-ducts has been advocated by McPhedran (16) and others. MacCallum, Miller, Rutherford, and many others are of the opinion that they arise as delicate sprouts from the interlobular bile-ducts, and that they represent an attempt to re-establish a connexion between isolated liver trabeculae and the duct system. Before attempting to draw any conclusions with regard to the nature and origin of these structures, we will briefly state what was observed by us in connexion with them. The epithelium lining the ducts stains well and deeply. The nuclei are large and show distinct nuclear membrane and chromatin network. We did not observe any mitotic figures, although Rutherford and Miller report having done so. When direct continuity can be observed between liver trabeculae and new bile-ducts the transition is quite abrupt. The deeply stained smaller cells of the ducts contrast sharply with the larger less deeply staining liver cells. The new bile-duct epithelium, although easily recognized from that lining the old ducts, resembles the latter much more closely than it does the liver cells. Where whole lobules have undergone degeneration, new bile-ducts can be traced in many instances almost as far as the central vein, but the zone immediately surrounding the latter structure contains no new ducts. In areas where partial destruction of lobules has resulted or where regeneration of liver tissue is evident, the new bile-ducts are found in large numbers in the periportal connective tissue between the liver trabeculae and the interlobular ducts. These observations upon the new bile-ducts, particularly their deep staining, the active nuclear structure, their resemblance to bile-duct epithelium, and their distribution around the interlobular ducts, all support the view that they have arisen by proliferation from the interrupted extremities of the old interlobular ducts.

Lindsay Milne (17) has attempted to show that the new bile-ducts 'are formed from a becoming evident of delicate normal bile-conducting channels which extend between the liver cells and the interlobular bile-ducts'. He says that 'In the centre of the liver trabecula runs a minute bile-collecting canaliculus which is lined by extremely fine flattened epithelium, and branches of which seem to extend round individual liver cells'. He maintains that after degeneration of

liver cells the epithelium of these fine canaliculi, which is more resistant than the liver cells to destructive agencies, swells up, thus 'producing the new bile-ducts. The acceptance of this theory must depend on the demonstration of this epithelium in the centres of normal liver trabeculae, and this he does not do. In the examination of large numbers of sections of normal human livers, we could find no evidence of the presence of such an epithelial lining to the bile canaliculus. In every instance where small bile-ducts could be traced to liver trabeculae there was no overlapping of the two types of epithelium and no extension of biliary epithelium into the centre of the liver trabeculae. If his view be correct, the new bile-ducts should not be found, as they are, chiefly at the periphery of the lobules, but should be distributed through all parts of the lobule.

A study of the development of the liver throws further light on this problem. The liver diverticulum arises at a very early period in embryos of about 3 m.m. from the junction of the yolk sac and the fore-gut. From the cranial end of this diverticulum the liver tubules rapidly develop. The caudal end becomes the gall-bladder and main ducts. There is from the first a marked difference between the epithelium lining the ducts and that forming the tubules, and the transition between the two is abrupt. This abrupt transition and marked difference in structure between the two types of epithelium has led many observers to the erroneous opinion that the two tissues are of different origin, the duct epithelium arising from hypoblast and the liver tubules from the mesoblast of the septum transversum. The liver tubules soon undergo a very rapid proliferation quite independently of the ducts, and for a time the majority are not connected with the duct system. At this stage the tubules have distinct lumina surrounded by cells, thus differing from the solid trabeculae of the adult liver. The ducts in the liver, unlike those of any other organ, arise by a secondary process from the larger ducts at the hilum. In embryos of 22.8 m.m. the development of the bile-ducts along the main branches of the portal veins has begun (Keibel and Mall (18)). They approach the liver trabeculae and establish communication with them. It will be seen, then, that during the normal process of development the liver cells at a very early period are sharply differentiated from the epithelium lining the ducts. The transition between the two is quite abrupt, and, further, the intra-hepatic ducts develop independently of the liver cells and only later establish communication with them. This, in conjunction with the evidence stated above, provides strong support for the view that after degeneration of liver cells regeneration takes place chiefly by multiplication of liver cells, and that the 'new bile-ducts' represent sprouts from older ducts growing out to establish communication with regenerated trabeculae in much the same manner as is seen during embryonic life. The fact that the bile-duct epithelium, although sharply differentiated from the liver epithelium at a very early stage, yet has the same origin, would indicate that regeneration of liver cells from new bile-ducts might be possible but not likely to be extensive.

It is a pleasure to acknowledge the help we have received from Dr. C. H.

Kellaway, Director of the Walter and Eliza Hall Institute of Research, in the preparation of this paper. We are also indebted to Drs. R. H. Strong and R. P. McMeekin for permission to investigate these cases.

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DESCRIPTION OF PLATES.

PLATE 8, FIG. 1. *Case I.* High-power view of liver, showing new bile-duct in continuity with regenerated liver cells, with young connective tissue containing numerous fibroblasts and lymphocytes. Haematoxylin and eosin.

FIG. 2. *Case II.* High-power view of liver, showing new bile-duct with club-shaped mass of liver cells at its termination. Haematoxylin and eosin.

PLATE 9, FIG. 3. *Case II.* High-power view of liver, showing regenerated liver cells arranged around distinct lumina. Haematoxylin and eosin.

FIG. 4. High-power view of liver, showing absence of trabecular arrangement, multinucleate liver cells, and grouping around lumina. Haematoxylin and eosin.

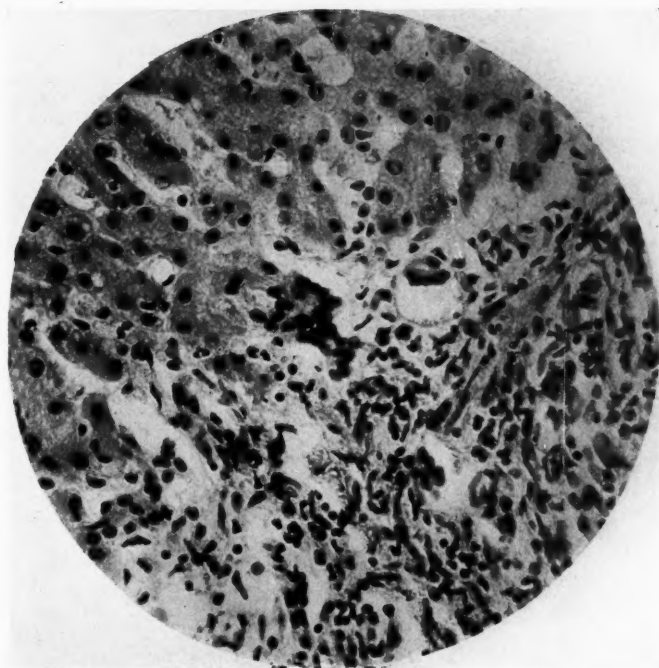


FIG. 1

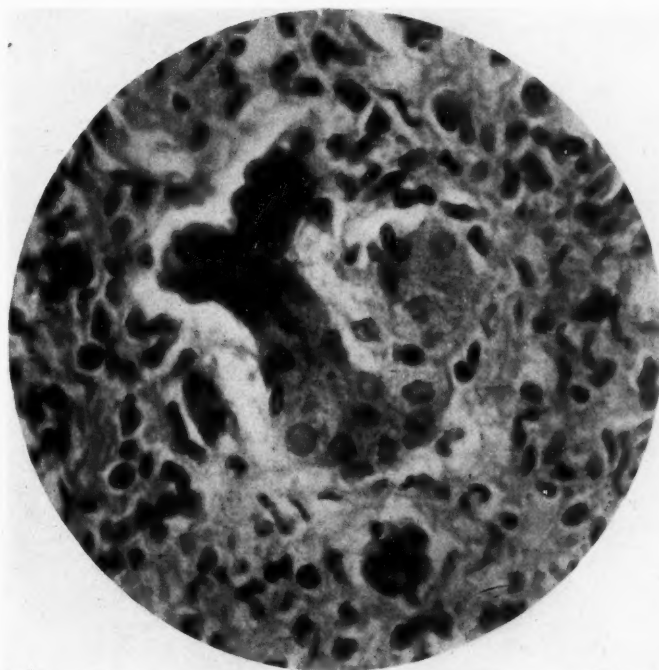


FIG. 2

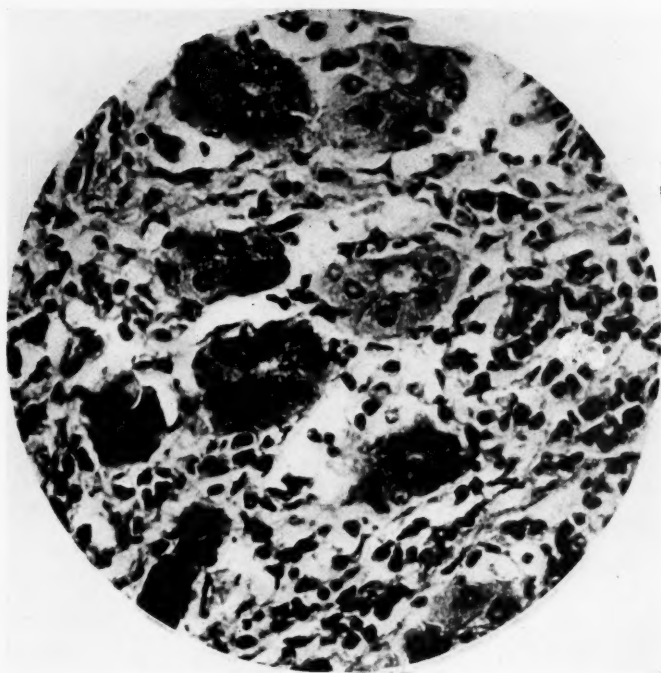


FIG. 3

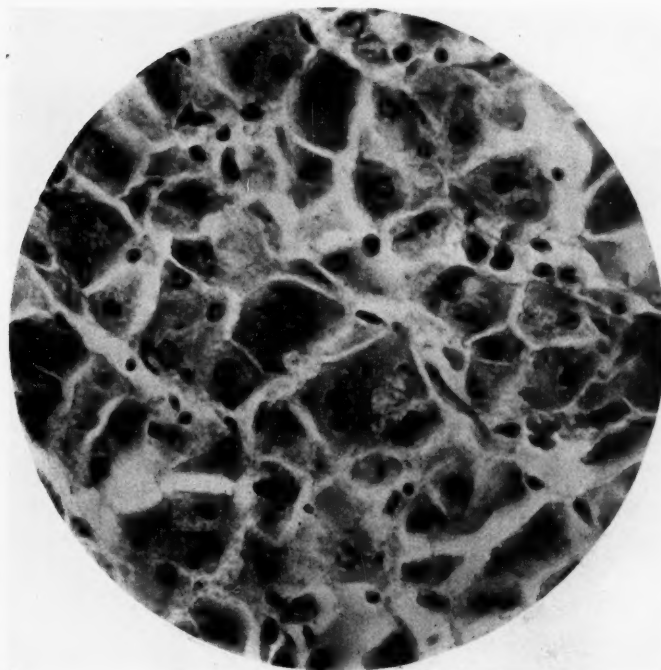


FIG. 4



THE DIAGNOSTIC VALUE OF DEXTROSE-TOLERANCE CURVES¹

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Introduction.

MANY workers have published papers purporting to show that the sugar-tolerance test can be used as an aid to diagnosis in diseases other than diabetes. We venture to make two criticisms of the bulk of this work: firstly, that it has been approached without sufficient study of the variations in the curve in health; and secondly, that most of the work has been presented in the form of small series of curves, each series applying to only a single disease, which procedure tends to give the impression that any abnormalities which such a series of curves may present occur only in that particular disease.

We have endeavoured to reduce these sources of error to a minimum: in the first place, by a careful study of a series of curves from healthy individuals; and, in the second, by placing all our curves found in various diseases in one large group. By this method, the question of the diagnostic value of the sugar-tolerance test is approached in a more rational manner, for it is possible to see if a particular type of curve is sufficiently limited to a single disease to be of any help in diagnosis. We have therefore divided abnormal curves into certain types.

The Types of Curve.

In a previous paper in this Journal (1) it was suggested that when Folin and Wu's (2) method was used with a dose of 50 gm. of dextrose taken by the mouth, the blood for analysis being obtained by pricking the finger, a sugar-tolerance curve should not be considered abnormal unless one or more of the following features were present:

- A. Fasting blood-sugar above 0.120 per cent. (if subject has been resting prior to test).

¹ Received March 2, 1927.

² A part of the expenses was defrayed out of the Parsons Research Fund, and the work was carried out during the tenure by one of us (W. W. Payne) of the Parsons Research Fellowship.

[Q. J. M., July, 1927.]

TABLE I.

Case No.	Sex	Time in Hours after giving Dextrose.										Dose of Dextrose.	Curve Type.	Diagnosis.
		0	$\frac{1}{2}$	1	1 $\frac{1}{2}$	1 $\frac{1}{2}$	2	2 $\frac{1}{2}$	2 $\frac{1}{2}$	3				
1	M	0.162	0.212	0.198	—	0.195	—	—	—	0.206	15	5	Diabetes	
2	M	0.156	0.212	0.227	—	0.241	—	—	—	0.196	15	5	"	
3	F	0.143	0.219	0.261	—	0.291	0.204	—	—	0.242	50	5	"	
4	M	0.214	—	—	0.266	0.282	—	—	—	0.244	25	5	"	
5	M	0.206	—	—	0.251	0.272	—	—	—	0.238	25	5	"	
6	M	0.123	—	—	0.236	0.222	—	—	—	0.176	25	5	"	
7	F	0.156	—	—	0.235	0.248	—	—	—	0.194	25	5	"	
8	M	0.333	—	—	0.389	0.400	—	—	—	0.382	25	5	"	
9	M	0.138	—	—	—	0.237	0.242	—	—	—	—	5	"	
10	M	0.43	—	0.312	—	0.285	0.240	—	—	0.187	—	5	"	
11	F	0.256	—	0.364	—	0.364	0.366	—	—	0.310	—	5	"	
12	M	0.124	—	0.212	—	0.225	0.234	—	—	0.206	—	4	"	
13	M	0.079	0.106	0.165	0.170	0.188	0.153	—	—	0.113	25	2	"	
14	M	0.114	—	0.173	—	0.164	0.145	—	—	0.111	15	1	"	
15	M	0.119	—	0.240	—	0.276	0.264	—	—	0.196	—	4	Glycosuria	
16	M	0.110	—	0.217	—	0.158	—	—	—	0.111	—	3	"	
17	M	0.108	—	0.214	—	0.143	0.096	—	—	0.090	—	3	"	
18	M	0.095	0.228	0.270	—	0.168	0.120	—	—	—	—	3	"	
19	M	0.112	—	0.197	0.197	0.151	—	—	—	0.070	3	H	Glycosuria and gastrojejunostomy	
20	M	0.073	0.172	0.240	—	0.240	—	—	—	0.096	1	1	Glycosuria	
21	F	0.115	0.224	0.271	—	0.230	—	—	—	0.208	4	4	Infantilism	
22	M	0.118	—	0.181	—	0.172	0.184	—	—	0.104	4	4	Suprapituitary tumour	
23	F	0.109	—	0.264	—	0.224	0.170	—	—	0.123	2	2	Definite Pituitary tumour	
24	M	0.087	0.214	—	0.214	0.224	—	—	—	0.079	4	H	Adiposity—probable	
25	F	0.087	—	—	0.100	0.110	—	—	—	0.098	1	1	"	
26	F	0.115	—	—	0.230	0.300	0.146	—	—	0.198	4	4	"	
27	F	0.096	0.152	—	0.191	0.183	—	0.128	—	—	2	2	"	
28	F	0.130	0.179	0.175	—	0.219	0.160	—	—	0.147	2	2	"	
29	F	0.103	0.142	0.240	—	0.204	—	—	—	0.100	4	4	Partial thyroidectomy and tetany	
30	M	0.115	—	—	—	0.240	0.177	—	—	0.138	4	4	Graves's disease	
31	F	0.123	0.200	0.221	—	0.240	0.177	—	—	0.095	4	4	"	
32	F	0.123	0.210	0.178	—	0.151	0.117	0.092	—	—	3	3	"	
33	M	0.117	—	0.177	0.177	0.123	—	—	—	—	1	1	Myxoedema	
34	M	0.097	0.231	0.245	—	0.219	0.151	0.101	—	0.088	4	H	Addison's disease	

Disorder of Pituitary
 {
 Definite
 Suprapituitary tumour
 Pituitary tumour
 Adiposity—probable
 }
 No evidence of
 Partial thyroidectomy and tetany
 Graves's disease
 Myxoedema
 Addison's disease

- B. Maximum blood-sugar above 0.20 per cent. in young adults, rising to 0.22 per cent. at the age of 70, and 0.24 per cent. at 80.
- C. Blood-sugar still above 0.120 per cent. at two hours in young adults, or at three hours at the age of 60 and over.

Considering these as the important features it would, theoretically, be possible to have eight types of curve, as follows :

	Number assigned to each Type of Curve.							
	1	2	3	4	X	Y	Z	5
Fasting Blood-sugar	N	N	N	N	A	A	A	A
Height of Peak	N	N	A	A	N	A	N	A
Return of Blood-sugar to Normal	N	A	N	A	N	N	A	A

N = Normal. A = Abnormal.

At one end of the scale there is the normal type of curve and at the other end the most abnormal, which is the well-known type commonly found in advanced diabetes. Of the intervening types marked X, Y, Z we have found no examples. In one or two instances we have found a fasting blood-sugar of slightly over 0.120 per cent. in cases other than diabetes, but the instances are so few and the excess is so slight, and so much depends upon what the subject was doing prior to the taking of the blood, that we have decided not to consider these as abnormal. We have found, therefore, five main types of curve, viz. :

- Type 1. Normal curve.
- Type 2. Normal fasting blood-sugar. Normal peak, but slow return.
- Type 3. Normal fasting blood-sugar. High peak, but a normal return.
- Type 4. Normal fasting blood-sugar. High peak, but slow return.
- Type 5. Abnormal throughout.

Mention must be made here of a further point which is an interesting feature of some curves, and that is the final descent of the blood-sugar to lower level than is usual. In our series of thirty-five curves from normal individuals, only six fell below 0.09 per cent. during the first three hours. In those suffering from certain diseases it will be found that a low figure in the final descent is very much more common. Curves which fall below 0.09 per cent. are marked with an H in the column referring to the types of curve.

Before setting out these curves in groups according to the type of curve, we would point out that our present purpose is to find out whether any one type of curve suggests any particular disease. The proportion of any one disease in a group must be considered in relation to the total number of that disease, as there are not equal numbers of each disease in any series. We have refrained from reporting percentage figures in respect of individual diseases, as such figures would be meaningless on account of the small numbers involved.

TABLE II.

	Groups, according to Type of Curve.					
	1	2	3	4	5	Total.
Diabetes	1	1	—	1	11	14
Glycosuria	1	—	3	1	—	5
Disorders of the pituitary: definite	—	1	—	3	—	4
probable	1	—	—	—	—	1
Adiposity	—	2	—	2	—	4
Graves's disease	—	—	1	1	—	2
Myxoedema and thyroidectomy	1	—	—	1	—	2
Addison's disease	2	—	—	1	—	3
Skin sepsis	2	1	1	—	—	4
Upper motor neuron lesions	3	1	4	1	—	9
Lower motor neuron lesions	3	—	2	1	—	6
Wasting not due primarily to diseases of C. N. S.	2	1	1	—	—	4
Muscular disorders of } Myasthenia gravis	3	—	5	1	—	9
indefinite pathology of } Chronic ophthalmoplegia	1	—	—	1	—	2

Curves of Sub-type H (in which the curve falls to below 0.090 per cent).

Glycosuria	1
Definite pituitary lesion	1
Upper motor neuron lesion	1
Lower motor neuron lesion	5
Addison's disease	3
Myasthenia gravis	6
Staphylococcal skin infection	1
Total	18

The contents of Group 1 show clearly the very important fact that a normal sugar-tolerance curve does not exclude any of the diseases included in our series, and inasmuch as all, or almost all, the diseases which are said to be characterized by an abnormal sugar tolerance are included in Table I, it may be said that a normal curve is possible in any disease.

Group 5 is the only group which contains a single disease, and it appears that a curve of this type is pathognomonic of diabetes.

Turning to the less important groups, Group 2 is a very small group. It is obviously an unusual type of curve, and it appears to have no particular significance.

In Group 3, containing over a quarter of the cases, there are three diseases represented by a greater number of curves than would be expected from chance alone: these are glycosuria, three out of five cases; upper motor neuron lesions, four out of nine; and myasthenia gravis, five out of nine. It is obvious, therefore, that this type of curve by itself has but little diagnostic value.

The conditions enumerated in Group 4 have only one curve each, except lesions of the pituitary, of which, out of a total of four cases, three fall in this group; but as there are eleven other curves representing ten different diseases, it cannot be said a curve of this type is any aid to diagnosis.

Sub-group H³ consists of eighteen curves with readings below 0.09 per cent. in the final descent; this occurred in about one-sixth of our curves from healthy subjects. Each curve has already appeared in Groups 1, 3, or 4.

Of the eighteen curves, fourteen are accounted for by three conditions, viz. lower motor neuron lesion, five out of a total of six cases; Addison's disease, three out of three; and myasthenia gravis, six out of nine. These proportions are very much more striking than any figures in Groups 1, 2, 3, or 4. It is possible that there is some common factor in these three diseases that causes this overaction of the sugar-storage mechanism. (See p. 467.⁴)

Discussion of Individual Diseases.

Diabetes. In our opinion, a subject giving a curve of Type 5 must be regarded as having diabetes mellitus, even if this curve is only found accidentally. A curve of another type, however, cannot be considered to exclude the diagnosis of diabetes if marked clinical evidence is present.

All the diabetic subjects have curves of Type 5 except three, viz. Nos. 12, 13, and 14. Case 14 was given only 15 gm. of glucose, and so cannot be discussed further. Case 13 had 25 gm., but the very low fasting value 0.079 per cent., and the final low figure 0.098 per cent. at four hours, of this patient are most unusual. The clinical evidence of diabetes was very strong. In 1920 he had glycosuria, thirst, and lassitude. These abated with diet, and he remained well until 1923, when he was unable to obtain a satisfactory diet as he was living in Cuba. The symptoms recurred, but on his return to England they again subsided with dietetic treatment. He had no glycosuria and no symptoms, except headache, when this test was made in 1924. In this connexion it is of interest to recall the case recorded by Enocksson (3), in which, three months after an attack of diabetic coma, a normal sugar-tolerance curve was obtained. On the restrictions in diet being removed, glycosuria returned, which could then only be controlled by a more limited diet.

Case 12 was a mild one, with a normal fasting blood-sugar. The reading was still over 0.20 per cent. at the end of three hours.

Glycosuria. Under this heading are included only subjects who were entirely free from any symptoms. From the mass of literature on this subject it seems to be generally believed that glycosuria with a normal curve is unimportant, but with any form of abnormal curve it should be regarded with suspicion, lest the patient become a diabetic. It seems that this view is unwarranted for the following reasons. Firstly, there are so many other diseases that are liable to give abnormal curves; secondly, curves of Type 3, which are the commonest to find in cases of glycosuria, show very definite evidence of an efficient storage mechanism; and, thirdly, it is now contended by Hatlehol (4)

³ In considering this sub-group it must be remembered that Folin and Wu's (2) method was used in all our sugar estimations. With other methods readings below 0.09 per cent. are common.

that the subsequent histories of cases of symptomless glycosuria do not suggest that they are likely to become diabetics. We submit, therefore, that glycosuria is of no consequence provided the sugar-tolerance curve is either normal or of Type 3.

Disorders of the pituitary. At the present time the diagnosis of disorder of the pituitary function is exceedingly difficult, and it is even harder to say of what type the disorder is, unless there be X-ray evidence of disease in the sella turcica or alteration in the visual fields. For this reason we have included in one group all the cases in which some disturbance of the pituitary function was suspected, irrespective of whether the evidence was in favour of hypo- or hyper-function of either the anterior or posterior lobe.

In Table III we have placed nine curves, supplemented by four others, which could not be included in the largest table as, either on account of the patient's age or of the circumstances of the test, no particular curve type could be assigned to them.

From these thirteen curves it will be seen that there is a general tendency towards a high rise and slow fall, no matter what the nature of the pituitary disturbance may be.

Gardiner-Hill, Jones, and Forrest Smith (5), in a paper on cases of obesity of suspected pituitary origin, found that there were two types of curve depending on the length of history of the condition. In cases in which the average length was two years the average rise was normal, but the fall was delayed. In cases of longer duration the average curve showed a smaller rise. The authors concluded from this that the sugar tolerance was increased. As their curves are only represented by an average curve, it is impossible to deny that some of their individual curves may have been unusually low, but their average curve is of a type quite commonly found in normal subjects, and it may be that, as the history of the case progresses, the sugar-tolerance curve becomes normal. It is a pity that their curves were not given in more detail, for it would have been interesting to see if any of the curves in cases of long-standing adiposity were unduly low, such as the curve from Case 24 in our series. In this case it will be noted that the symptoms were of much longer duration than in any of the others. These authors have also obtained repeat curves in some cases under treatment, and use the changes found in the curves as a guide to the progress and treatment. It is difficult to derive much satisfaction from their findings, as in many cases the changes they report are no greater than may be found in repeat curves from healthy subjects (1, 6). In this connexion the repeat curves from Case 27 may be given:

Dose, 100 grm., 0, 0.118; $\frac{3}{4}$ hr., 0.193; $1\frac{1}{2}$ hr., 0.215; 3 hr., 0.142.

" " " 0, 0.108; $\frac{3}{4}$ hr., 0.183; $1\frac{1}{2}$ hr., 0.150; 3 hr., 0.135.

The interval between these two curves was three days, and during that time no treatment was given.

Major (7), out of eight cases of adiposity of possible pituitary origin, found

TABLE III

Case No.	Sex.	Age.	Weight in lb.	Duration in Years.	Time after taking Dextrose.							Remarks.	
					0	$\frac{1}{2}$	$\frac{3}{4}$	1	$1\frac{1}{2}$	2	$2\frac{1}{2}$		3
20	M	18	70	4	0-073	0-172	—	0-240	0-218	—	—	0-208	Infantilism. ? Suprapituitary growth
21	F	48	118	2	0-115	0-224	—	0-271	0-230	0-184	—	0-104	Suprapituitary tumour
22	M	16	81	5	0-118	—	0-181	—	0-172	—	—	0-123	Infantilism. ? Traumatic injury to pituitary. Loss of sight in right eye and the temporal field of left
23	F	27	98	4	0-109	0-214	—	0-264	0-224	0-170	—	0-079	Definite pituitary tumour. X-rays show large sella turcica. Visual fields very much reduced
70	F	12	56	$\frac{1}{2}$	0-135	0-234	0-222	0-164	0-155	—	0-132	—	Acromegaly. Diabetes
71	F	50	140	5	0-120	0-182	—	0-213	—	0-155	—	—	Definite cerebral tumour. ? Pituitary. X-rays show sella turcica enlarged
72	F	51	—	10	0-298	0-326	—	0-353	0-335	—	—	—	Acromegaly (active). Left paracentral scotoma
24	M	25	366	18	0-087	—	0-100	—	0-110	—	—	0-098	Adiposity. ? Hypopituitary. X-rays show small sella turcica
73	M	10	90	3	0-119	0-220	—	0-225	0-169	0-156	—	—	? Hypopituitary
25	F	30	224	'Some'	0-115	—	0-230	—	0-300	—	—	0-198	Adiposity with no evidence
26	F	17	229	$\frac{4}{4}$	0-096	0-132	—	0-175	0-146	0-146	0-128	—	Adiposity of a deranged
27	F	35	252	'Many'	0-130	—	0-191	—	0-183	—	—	0-147	Adiposity pituitary function
28	M	45	252	25	0-103	0-179	—	0-240	0-219	0-160	—	0-100	Adiposity

four who gave curves showing a high rise and a slow return to normal. The remaining four were normal.

Paullin and Sauls (8) investigated the curves in twenty-six cases of adiposity, of which pituitary lesion was only suggested in one. Five of these gave curves of Type 5, and were considered to be definite cases of early diabetes; of the remaining twenty-one, ten gave normal curves.

Before passing on to pituitary lesions unassociated with adiposity we must summarize the evidence of the value of the test in determining whether the pituitary is involved in obese subjects. In view of the fact that Paullin and Sauls found five cases of diabetes in their series of twenty-six cases of adiposity, and of the well-known work of Joslin (9) on the relation of obesity to diabetes, the finding of a high peak and slow return in the sugar-tolerance curve of an obese subject cannot be said to point to a pituitary lesion in the absence of any clinical evidence. On the other hand, since most definite cases of pituitary lesion tend to have an abnormal curve, the finding of a normal curve may be considered to weigh against there being any abnormality of the pituitary function.

None of our six patients with definite evidence of pituitary lesion were unduly heavy. Only one showed a normal curve, and she was a case of acromegaly of five years' duration. The remaining five all gave curves showing a slow return to normal, and four of these had high peaks. There are no curves of Type 3. This is of interest, as it is the commonest type of abnormal curve.

The remaining three cases in the table had some symptoms suggestive of pituitary disorder, but, as proof was lacking, their curves cannot be considered as evidence in our endeavour to find the changes produced by a pituitary lesion. However, neither among these nor among our four obese subjects is there a curve of Type 3.

Thus the information obtained from this small series is merely negative, but none the less useful. A curve of Type 2 or 4 by no means proves that the pituitary is at fault, but is consistent with the diagnosis of active trouble in this region. A curve of Type 1 or 3 is definitely against such a diagnosis. These suggestions, in the main, fall in with the findings of other workers.

Disorders of the thyroid. It is seldom that a sugar-tolerance curve is required as an aid to diagnosis of disorders of the thyroid, as cases are usually straightforward on clinical evidence, and, if help is needed, the finding of the basal metabolism is of more value. It is fortunate that this is so, for the sugar-tolerance curves are most unsatisfactory in these conditions. Many cases give normal curves, and those that do not show a tendency to a high peak and slow return to normal irrespective of whether this disorder takes the form of hypo- or hyper-thyroidism (7, 10, 11). The only satisfactory group of cases of myxoedema that we have found is that of Gardiner-Hill, Brett, and Forrest-Smith (12). In this series, if the age of the patients is taken into account, many of the curves are normal. Our own cases are too few for useful consideration.

Addison's disease. The curves from three cases of this disease are of interest chiefly on account of the rarity of the condition. Otherwise, the only point

worth noting is that they all show marked hypoglycaemia. Cases 33 and 34 were definite, and the diagnosis less certain in Case 35.

Skin sepsis. The connexion between diabetes and staphylococcal infections of the skin has been recognized for many years. It is of interest, therefore, to see the effect of this condition on the sugar-tolerance test. Of our four cases, Nos. 36 and 37 gave abnormal curves. No. 36 gave a normal curve when the sepsis had cleared up.

Disorders involving voluntary muscles. Our reason for presenting this somewhat miscellaneous group is that the muscles are known to play an important part in the use and storage of sugar. This section of the work was undertaken to see if disordered conditions of the muscles had any effect on the sugar-tolerance curve, and not in the hope that a particular type of curve would prove to help in the diagnosis of muscular disease. As there are not enough cases of individual diseases to consider each separately, we have adopted a classification as follows:

1. Upper motor neuron lesions.
2. Lower motor neuron lesions.
3. Wasting not due primarily to disease of the central nervous system.
4. Muscular disease of indefinite pathology.

Taking this group as a whole it will be seen that out of thirty cases only twelve have normal curves, and by far the commonest abnormality is a curve of Type 3.

Although the incidence of various types of curve appears very similar in both upper and lower motor neuron lesions, when we come to consider the phenomena of terminal hypoglycaemia we find a very marked difference. In the sub-group of upper motor neuron lesions only one curve out of nine shows hypoglycaemia at three hours (as against roughly one in six in normal individuals (1)), but five out of six curves from cases of lower motor neuron lesions show this peculiarity.

Myasthenia gravis. As we have nine cases of this comparatively rare disease we have felt justified in considering them separately. Six of the patients gave definitely abnormal curves, and the remaining three all showed a low reading at three hours. This is the only disease in this group in which we venture to suggest that the sugar-tolerance test is of any help in diagnosis. A curve that shows neither a high peak nor terminal hypoglycaemia would, in our view, weigh against a diagnosis of myasthenia gravis, and a curve showing both these features would support such a diagnosis. Williams and Dyke (13) have reported blood-sugar curves from three cases of myasthenia gravis. In each case they found that the curve had no abnormally high peak with a dose of 50 gm. of glucose, but all the curves were very markedly higher when the dose was increased to 100 gm. On the assumption that in a healthy individual a dose of 100 gm. does not commonly produce a higher peak than 50 gm., and that the only result of a larger dose is slightly to delay the fall of the curve, these workers conclude that there is 'a defective carbohydrate metabolism in this disease, the defect probably being located in the muscles'. As they did not continue the test

for three hours, it is not surprising that they did not observe any hypoglycaemia. It is of interest to note that one of the curves of Type 1 (No. 67) is almost certainly from the same man as Case 1 in their paper.

The Relation of Hypoglycaemia to Muscular Fatigue and Exhaustion.

Attention has already been called to the fact that a very large proportion of curves showing hypoglycaemia after the peak has been reached are from three pathological conditions, viz. lower motor neuron lesion, Addison's disease, and myasthenia gravis. The figures given on p. 462 are so striking that we have made an effort to collect other conditions under which this type of hypoglycaemia occurs. We have already mentioned the fact that we found it in six out of thirty-five curves from healthy subjects. In our three experiments in which dextrose was injected directly into the duodenum (1), decidedly low readings are shown at the end of the curve in each case (viz. 0.085 per cent., 0.080 per cent., 0.081 per cent.). In our present series, Case 18, who had a gastrojejunostomy, gave a reading of 0.070 per cent. at three hours. In this case symptoms similar to those seen after an overdose of insulin were experienced by the patient. Levine and his co-workers (14, 15) have reported hypoglycaemia in samples of blood taken from athletes after a Marathon race. Hypoglycaemia was only found in those runners who were collapsed, and the greater the collapse the more marked was the hypoglycaemia.

Clark (16) has found hypoglycaemia in experimental animals when the vagus has been stimulated, and he states that it is more marked and more constant when the sympathetic has been paralysed. From this observation it appears that hypoglycaemia can be due either to the stimulation of the vagus, or to the paralysis of the sympathetic. It has been suggested that the fall in a sugar-tolerance curve is due, at least in part, to the stimulation of the pancreas by the vagus, this stimulation being caused by the high concentration of sugar in the blood. If this hypothesis be correct, the hypoglycaemia in the three experiments with the duodenal tube and in the patient with a gastrojejunostomy might be due to the excessive stimulation of the vagus in this way. On the other hand, in the case of the long-distance runners, it is probable that exhaustion of the sympathetic or the suprarenals is the underlying cause of the hypoglycaemia, since it is hardly likely that in the two or three hours of the race the food stores of the body would be entirely depleted. The fact that adrenalin is as effective as sugar in the treatment of insulin hypoglycaemia also tends to strengthen this view, and it is further supported by the finding of hypoglycaemia in our cases of Addison's disease, and by the statement of Marañón (17) that sufferers from this disease are markedly hypersensitive to insulin.

We would suggest, therefore, that when hypoglycaemia is seen at the end of a sugar-tolerance curve it is likely that an explanation may be found either in the excessive stimulation of the vagus or in some derangement of the sympathetic.

Lower motor neuron lesions and myasthenia gravis are the only two condi-

tions among the above mentioned in which the hypoglycaemia cannot be accounted for readily by one of these explanations. In both these conditions there is a high proportion of curves with abnormally high peaks, and of those that are not definitely abnormal in this respect all but one show peaks near the upper limit of the normal range. Therefore it seems possible that the hypoglycaemia is caused by the over-stimulation of the vagus in these cases.

These suggestions are not, at first sight, in agreement with the work of Graham (18), who reported changes in his own sugar-tolerance curve when he was fatigued. Hypoglycaemia was not among the changes found by him. The word 'fatigue' is used by him to describe the condition of a man who needs a holiday, and cannot therefore be compared physiologically with the state of 'exhaustion' in a man who has just completed a Marathon race.

Other Conditions in which Abnormalities in the Sugar-tolerance Curve have been reported.

Apart from the diseases already mentioned, there are, undoubtedly, many other pathological conditions in which an abnormal sugar-tolerance curve may be found.

Friedenwald and Grove (19) recorded the results of a large number of sugar-tolerance tests from cases of carcinoma, and considered that the abnormalities found (a high rise and a slow fall) were of value in the diagnosis of this disease. No ages were given. Biermer (20), however, in a similar series, found no constant variation from the normal; indeed, if due allowance be made for age, only about one-third of his cases show any kind of abnormality.

Major (7) and Williams and Humphreys (21) found abnormal curves in nephritis in the acute stage and in cases with urea retention.

Strouse (22) found a 'diabetic type' of curve in a case of cirrhosis of the liver.

Pemberton (23) has found a curve with a high peak and slow fall in cases of rheumatoid arthritis.

Drury and Farran-Ridge (24) have found a considerable number of markedly abnormal curves amongst the inmates of a mental hospital, many being of Type 3 (aptly called by the authors a 'church steeple curve').

Summary.

At present we consider that the only type of curve from which a definite diagnosis can be made is Type 5. If a patient has a curve of this type he has diabetes. In no other instance should the type of curve be allowed to outweigh definite clinical evidence. In some cases in which the clinical evidence leads to doubt as to the diagnosis, the sugar-tolerance test may be of value, but only where the differential diagnosis lies between a condition in which the curve is commonly abnormal and one in which it is usually normal. Thus it is of help

in deciding whether an obese patient is suffering from a pituitary tumour, diabetes, or merely simple adiposity. Another example is in the differential diagnosis between hysteria and myasthenia gravis.

For the most part, though the findings in various diseases are of considerable scientific interest, we fear that the sugar-tolerance test is of little value in differential diagnosis at the bedside.

Our thanks are due to Dr. J. H. Ryffel for the use of his laboratory, to the staffs of Guy's and Lambeth Hospitals for permission to investigate their cases, and especially to Dr. C. P. Symonds, who, in addition, gave us much valuable criticism and help.

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STUDIES IN BLOOD COAGULATION AND HAEMOPHILIA¹

I. BLOOD COAGULATION IN HAEMORRHAGIC DISEASES

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It has long been known that whereas in many diseases the coagulation time of the blood may be a true index of the haemorrhagic tendency, in others it is not. Thus in most cases of jaundice and purpura, where there is a proven coagulative deficiency, the coagulation time is normal. In the following observations the coagulation times have been taken, not only of the first drop of blood, but also of successive drops from a single puncture, in accordance with the

COAGULATION CURVE WITH LIMITS OF NORMAL VARIATION.

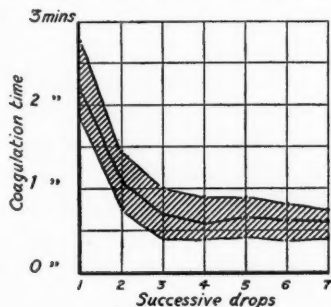


FIG. 1.

method described by Gibbs, and the results plotted in a curve (Fig. 1). (Details of the procedure and the coagulometer used may be found in his original article (1).)

Thus not only do we find the spontaneous coagulability of the blood, but also an index of the reaction of the blood and tissues against haemorrhage. It is not the first drop of blood from a wound which stops haemorrhage; it is the blood which has been rendered more coagulable by the many influences brought into play when the wound was made.

From what is known at the present time, we would divide this reaction into two main groups, the tissue reaction and the platelet reaction.

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1. *Tissue reaction.* The bruising of any cellular tissue liberates a thromboplastic substance (thrombokinase) necessary to the clotting of blood and acting quantitatively, i. e. the greater the amount present the more rapidly will clotting take place (Howell (2), Addis (3), Mellanby (4), &c.).

2. *Platelet reaction.* There is a popular belief that the role of the blood-platelets in coagulation has been discredited, but a survey of the literature on the subject will show that there is no foundation for this. Even Pickering (20, 21, 22), who with his colleagues claims to have shown that thrombocytes are not essential to coagulation, admits that 'they must play an important part in arresting haemorrhage' (23).

It has been definitely shown (Duke (5), Hayem, and others) that when blood is shed the platelets agglutinate into masses or become adherent to the injured intima of the blood-vessels. The action of this mechanism can be demonstrated long before the laying down of fibrin has commenced. It has also been shown (Morawitz (6), Bayne-Jones (7), Howell (8), Austin and Pepper (9)), that on disintegration these platelets liberate free prothrombin in large quantities, and a smaller amount of thromboplastic substance (thrombokinase). Thus the platelets will tend to stop haemorrhage, first by their mechanical agglutinating properties, and secondly by concentrating the supply of prothrombin and thromboplastic substance (thrombokinase) at the bleeding surface.

By the method of taking the coagulation time of successive drops of blood, we can trace this mechanism from start to finish, and can show any deficiency in the coagulability of the blood, the tissue reaction, or the platelet reaction. Thus the coagulation time of the blood is shown in the first drop; the next one or two drops are an index of the tissue reaction; and subsequent drops are an index of the platelet reaction. It is not suggested that the tissue reaction stops after the second or third drop, but merely that its action must become less and less marked, since the tissues were only once bruised, and that before the first drop was taken. The platelets, on the other hand, are becoming more and more concentrated round the bleeding surface, thus concentrating the supply of prothrombin, and also liberating an increasing amount of thromboplastic substance (thrombokinase). Thus, although the tissue reaction must diminish in intensity after a while, the coagulability of the blood coming from the wound does not decrease, since the platelet reaction is taking the place of the tissue reaction.

The normal initial coagulation time by this method varies from 1 min. 40 sec. to 2 min. 50 sec., with an average of 2 min. 8 sec. from 198 adult cases with no haemorrhagic history, taken at random in a surgical ward. (Personal communication—Miss Croskery.) The average coagulation curve is shown in Fig. 1, the shaded area denoting the normal limits of variation as found in 30 adult medical cases with no history of haemorrhage. The main cause for this comparatively slight variation is evidently the texture of the patient's skin, a fine skin giving slightly higher readings than a coarse one.

The time that elapses between the taking of the drops of blood undoubtedly

affects the coagulation time of each individual drop. Since in the taking of these curves only one coagulometer was used, this interval varies considerably in each curve and in different parts of the same curve, but we have found that this does not affect the ultimate character of the curve taken as a whole.

Since a graduated vaccino-style was used to make the stab wound, the puncture would be broader than that made by the needle used by Gibbs. It is for this reason that the coagulation times obtained by him were shorter than those published in this article.

Purpura.

It has been shown that in a large majority of cases of purpura the blood-clotting elements are normal in quantity and quality, the coagulation time remaining unaffected and the only change in the blood being a very marked diminution of blood-platelets, with an increased bleeding-time (Howell (2), Hess (10), Duke (5, 11), Pratt (12), Bedson (13), &c.). Why this denudation of the blood of its platelets should not cause any decrease of prothrombin in the blood has been explained by Hess (10), who has shown that the platelets are merely broken up, their constituent parts passing into solution in the blood. This explains why the actual coagulation time should remain normal. The platelet reaction, however, as defined above, must necessarily be deficient. The coagulation curve is typical (Figs. 2, 3, 4, 5, and 6).

In all but one of the cases described the initial point was within normal limits, denoting a normal coagulation time. And, in all, the second point fell in the normal manner, thromboplastic substance (thrombokinese) having been added from the tissues. Subsequent points, however, remained well above the normal limits, there being practically no platelet reaction, and consequently no concentration of prothrombin or platelet thromboplastic substance (thrombokinese).

It must be noted that in purpura, as in jaundice, the coagulation curves of many patients in whom the symptoms were not very pronounced were within normal limits, although definitely above the average.

Case V (Fig. 6) is of special interest in that, when first observed, his clinical picture was highly suggestive of a simple purpura haemorrhagica, and his coagulation curve was almost exactly the same as that found in Fig. 4. Coincident with the aplastic change in his blood picture, however, there was a progressive uniform elevation of his coagulation curve, till just before death we have the curve shown in Fig. 6. As we would expect, the aplastic change must have been accompanied by a decreased formation of platelets. This would produce a quantitative deficiency of prothrombin, which, superimposed on the lysis of what platelets were formed, would account for the very abnormal nature of the curve. Unfortunately, no estimation of the prothrombin content was possible, but the coagulation curve definitely indicates that there was some deficiency in the coagulative elements.

PURPURA.

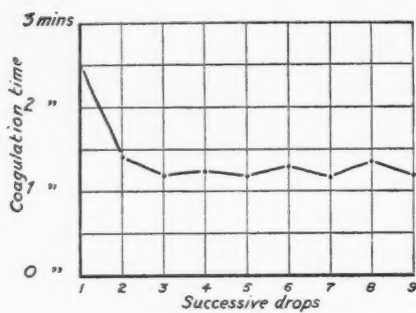


FIG. 2 (Case I).

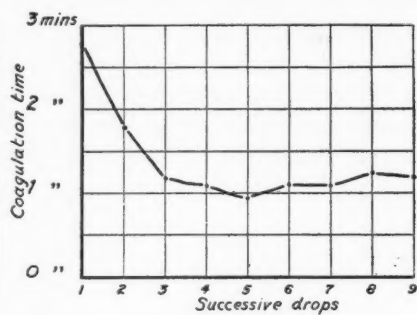


FIG. 3 (Case II).

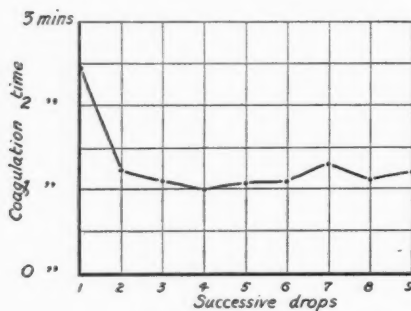


FIG. 4 (Case III).

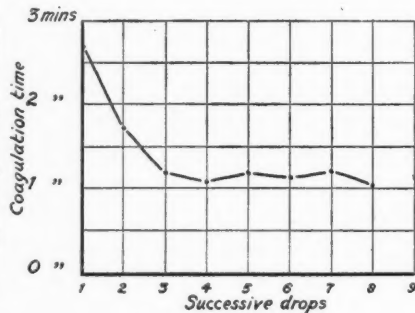


FIG. 5 (Case IV).

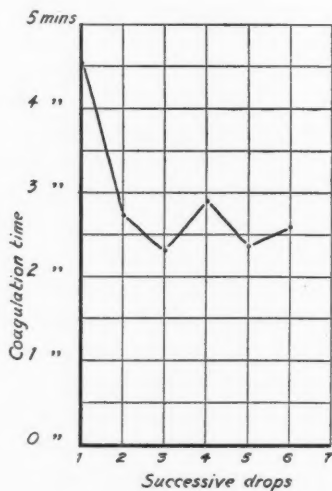


FIG. 6 (Case V).

It has been observed by others that an increase of the coagulation time in purpura is a bad prognostic sign, and I would suggest that it always denotes this aplastic change wherein there is a deficiency of platelet formation superimposed on the platelet destruction found in simple purpura.

Jaundice.

The cause of the haemorrhagic tendency in jaundice has not yet been satisfactorily explained, although many theories have been advanced (Morawitz (14), Whipple (15), &c.). It has been definitely established that in certain cases of extreme liver inefficiency the amount of fibrinogen in the blood is diminished (Whipple (15)), but this by no means applies to all cases of jaundice. Many of

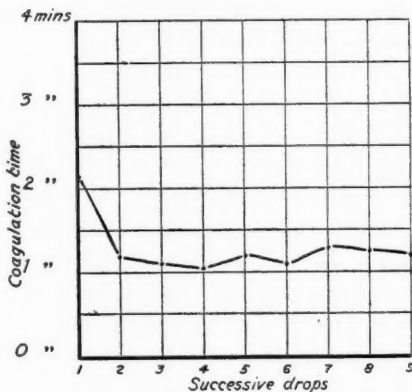


FIG. 7 (Case VI).

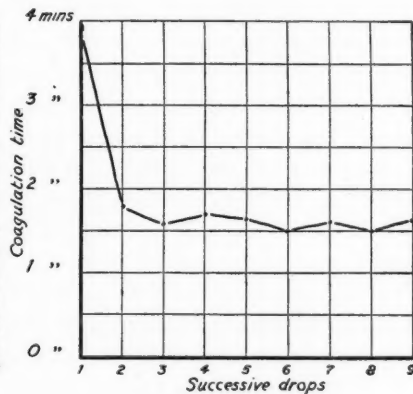


FIG. 8 (Case VII).

those cases of obstructive or simple catarrhal jaundice, which are such a menace to the surgeon, have been shown to have a normal coagulation time (Duke (11)). The coagulation curves, however, as shown in two cases examined of deep jaundice (Figs. 7 and 8), show a definite abnormality, almost identical with that found in purpura, suggesting that the haemorrhagic tendency is due to a deficient agglutination of the platelets. It seems rational that this should be so, since, as far as we know, the agglutination is purely a physical process, which might readily be prevented by the lowering of surface tension produced by the presence of bile salts in the blood. The absence of any purpuric symptoms would then be explained by the experiments of Bedson (13), who showed that two factors are essential in the production of purpura—diminution of platelets and the presence of a toxin which will damage the capillary endothelium. I would suggest that in jaundice this toxic factor is absent except in those isolated cases where definite purpuric symptoms do appear (Duke (11)).

In Case VII (Fig. 8) the increased initial coagulation time and associated heightening of the whole curve will be due to the lack of fibrinogen shown by

Whipple (15) to occur in cases of marked liver inefficiency. It is interesting to note that this curve corresponds very closely to Case V (Fig. 6), where there was also a quantitative coagulative deficiency in the blood, superimposed on a deficient platelet reaction.

Haemophilia.

All observers agree that a marked prolongation in the coagulation time of the blood is a constant feature in this disease, and practically all the clotting elements have been blamed in turn for this defect. Thus a deficiency of thromboplastic substance (thrombokinase) (Sahli (24), Morawitz and Lossen (25), Nolf and Herry (26)), calcium (Wright), and an excess of antithrombin (Weil, Feissly (27)) have been said to be the causal factors, but more recent investigators have been unanimous in putting it down to some defect in prothrombin, whether it be quantitative (Howell (2), Hurwitz and Lucas (16), Klinger (28)) or qualitative (Addis (17), Sajous (18), Minot and Lee (19), Wöhlisch (29), Christie, Davies, and Stewart (30)). Pickering and Gladstone (31, 32) have recently advanced the theory that it is due to an excess of protective colloid in the prothrombin-fibrinogen complex. Christie, Davies, and Stewart have to a certain extent confirmed the work of Howell and Minot and Lee, and have gone on to show that the abnormality in haemophilia is an undue functional stability of many of the formed elements of the blood, revealing itself, from a coagulative point of view, in the slow liberation of prothrombin from the blood-platelets, and also the slow formation of thrombin from prothrombin.

Now what effect will this have on the coagulation curve? As was found by Gibbs in his single case of haemophilia, I found a high initial coagulation time, followed by the usual fall, and then a rise, in some cases to well above the original level, this being constant in numerous observations in six of the eight cases of true haemophilia examined (Figs. 9, 10, 11, 12). Here the initial coagulation time will be lengthened by the slow liberation of prothrombin. The thromboplastic substance (thrombokinase), of which it has been proved there is no deficiency, will then cause the curve to fall by the law of mass action. The subsequent rise seems to indicate some definite deficiency in the platelet reaction superimposed on the slow liberation of prothrombin, but we have not been able to demonstrate experimentally any defect in the agglutinating properties of the platelets.

In the two other cases of haemophilia examined, the prolongation of the coagulation time was so great as to make the end point on Gibbs's coagulometer impossible to determine. This was evidently due to the fact that, even after coagulation had commenced, it proceeded so slowly as to allow of the formation of small particles of fibrin, which ultimately formed a suspension in the revolving drop of serum.

HAEMOPHILIA.

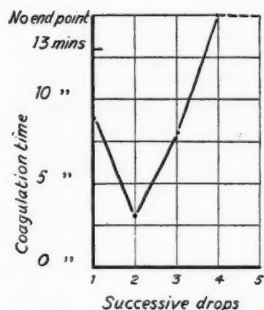


FIG. 9 (Case VIII).

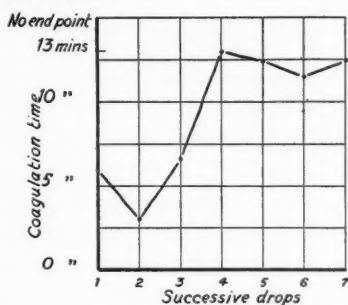


FIG. 10 (Case IX).

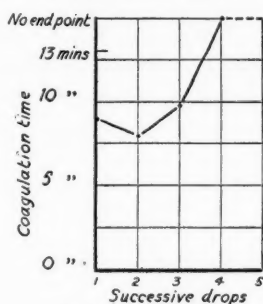


FIG. 11 (Case X).

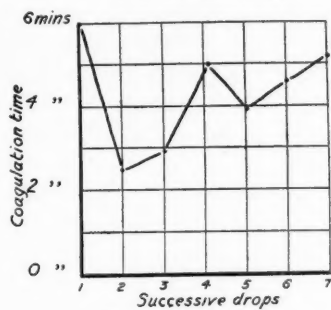


FIG. 12 (Case XI).

PSEUDO-HAEMOPHILIA.

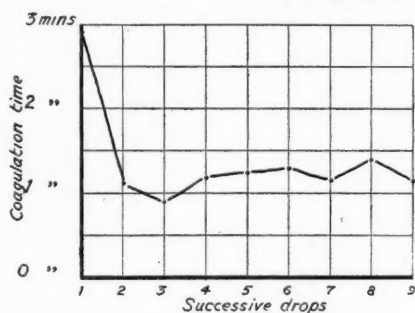


FIG. 13 (Case XII).

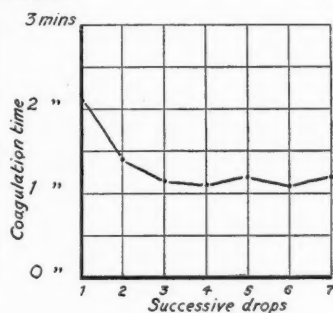


FIG. 14 (Case XIII).

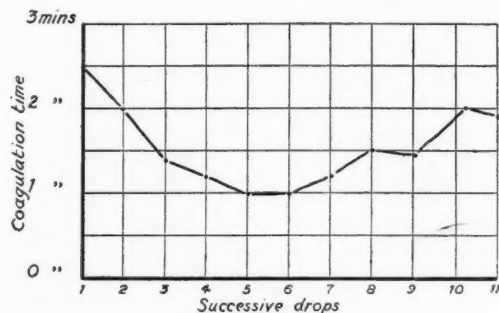


FIG. 15 (Case XIV).

Pseudo-haemophilia.

Lastly, we come to those cases where, with no haemorrhagic family history, there is a definite tendency to haemorrhage after injury. In eight cases examined with histories of excessive haemorrhage the coagulation curve was abnormal in three (Cases XII, XIII, XIV) and normal in five. Of the normal five, three had minor operations performed upon them subsequent to the taking of the coagulation curves, with no excessive haemorrhage.

Unfortunately, neither time nor circumstance permitted of a thorough blood examination in those cases which showed an abnormal curve, so we can only submit the curves (Figs. 13-15) as a possible method of differentiating these dangerous cases from the much larger class where there is no contra-indication to operation.

It is interesting to note that in one of the cases (Case XIV) the curve (Fig. 15) has a slight but definite haemophilic tendency, showing a rise after the initial fall. In this case, although there was a definite haemorrhagic history, the coagulation time was normal, but the coagulation curve was very definitely abnormal.

Conclusions.

1. By taking the coagulation time of successive drops of blood from a single stab wound, we get not only the coagulation time of the blood, but also an index of the tissue reaction and platelet reaction, and thus a true index of the haemorrhagic tendency.

2. In haemophilia we get a characteristic curve, indicating a deficiency in the coagulative elements of the blood, and also a deficiency of the platelet reaction.

3. In severe purpura and jaundice we get a characteristic curve, indicating a deficiency of the platelet reaction.

4. Three cases are described where, although there is a definite haemorrhagic history, the coagulation time is normal. The coagulation curve in these cases is definitely pathological.

Case Reports.

Case I. M. E., female, aged 12. History of intermittent febrile attacks, accompanied by vomiting, colicky abdominal pain, and slight pain and swelling in ankle, rapidly followed by the appearance of a dense purpuric rash on trunk and limbs with occasional epistaxis. Examined during severe attack with extensive purpura and epistaxis. Platelets in film very scanty.

Case II. E. Y., female, aged 22. History of 'influenza', followed by appearance of purpuric rash on legs, and painful joints. Rash soon spread to trunk, and to lesser extent to arms. Slight epistaxis.

Case III. A. P., male, aged 35. Blood picture typical of acute lymphatic leukaemia. Blood-platelets (with Pratt's soln.) 30,000. Haemorrhage from nose and gums. Purpuric rash over trunk and upper extremities. Haemorrhage into retina.

Case IV. W. B., male, aged 25. Admitted with history of attack simulating influenza, followed by appearance of purpuric rash on neck, chest, and limbs, and haemorrhage from gums. Blood picture typical of acute lymphatic leukaemia. Bleeding-time over twelve hours (prick on lobe of ear). Blood in stools and urine. Retinal haemorrhages. Death $3\frac{1}{2}$ weeks after onset. *Post mortem*: acute lymphatic leukaemia confirmed.

Case V. J. T., male, aged 13. Admitted with history of febrile attack followed by oedema of face, haemorrhage from gums and nose, and the appearance of a purpuric rash on limbs. Blood picture: haemoglobin 12 per cent. with colour index of 1.1; 40 per cent. lymphocytes with a few myeloblasts. Platelets 60,000. After blood transfusion slowly improved, but Hb never rose above 20 per cent. Readmitted six months after first attack with temperature, bleeding from nose and gums, and purpuric rash all over body. Blood picture typical of aplastic anaemia. Went rapidly downhill and died three weeks after admission. *Post mortem*: typical of aplastic anaemia.

Case VI. B. H., male, aged 69. Simple catarrhal jaundice. No temperature. No haemorrhage. Jaundice very deep. Complete recovery under medical treatment.

Case VII. M. R., female, aged 39. Typical acute yellow atrophy. Positive van den Bergh. Leucin and tyrosin present in urine. Deeply jaundiced. No haemorrhage of any kind.

Case VIII. J. C., male, aged 25. *Family history.* Definite of haemophilia for one generation (previous family history not known); four definite cases in family, and four indefinite (died in infancy). *Symptoms.* Bruises easily; typical haemorrhage into joints, gums, and nose. Very severe haemorrhage from trauma on four occasions, once almost fatal.

Case IX. G. M., male, aged 7. *Family history.* Definite of haemophilia for two generations, five definite cases in family. *Symptoms.* Bruises easily; typical haemorrhages into joints and gums; almost fatal haemorrhage from scalp injury.

Case X. J. M., male, aged 40. *Family history.* Definite of haemophilia for five generations, twelve cases on record. *Symptoms.* Bruises easily; typical haemorrhages into joints, kidneys, and gums; numerous severe haemorrhages after trauma.

Case XI. J. C., male, aged 20. *Family history.* Definite of haemophilia for one generation only, three haemophilic brothers, one haemophilic cousin. *Symptoms.* Bruises easily; frequent epistaxis and bleeding from gums, sometimes leading to severe anaemia; very severe haemorrhage from trauma on three occasions, once almost fatal. No haemorrhage into joints. A comparatively mild haemophilic.

Case XII. A. B., male, aged 30. No family history of bleeding. Tooth pulled nine months ago, haemorrhage excessive, and socket still bleeds when teeth are brushed. Tonsillectomy three weeks ago, haemorrhage very excessive, and still occasional bleeding. Hernia operated on one week ago, haemorrhage not excessive, but haematocoele rapidly developed afterwards.

Case XIII. W. Y., male, aged 35. No family history of bleeding. Always bleeds freely from shaving cuts. Can only remember having had one accident, when he cut his hand; the wound bled for over a day, a considerable amount of blood being lost. Has had teeth pulled twice; on both occasions great difficulty was experienced in controlling haemorrhage, the gums bleeding on one occasion for four days, and on the other for seven days.

Case XIV. W. D., male, aged 40. No family history of bleeding. Has always bruised very easily and sometimes extensively, and has been led to believe on this account that he has a 'thin skin'. Gums frequently bleed (no pyorrhoea). Has only had one accident that he can remember, when his front teeth were loosened. At this time his gums bled for seven days, leaving him very weak and anaemic. Inguinal hernia operated on seven days previously, haemorrhage excessive, and there was a large haematoma at the site of operation.

In conclusion, I must thank Prof. G. Lovell Gulland for the trouble he has taken in collecting suitable cases, and for his permission to publish them. Without his co-operation it would have been impossible to investigate such a comprehensive series of cases.

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STUDIES IN BLOOD COAGULATION AND HAEMOPHILIA¹

II. OBSERVATIONS ON HAEMIC FUNCTIONS IN HAEMOPHILIA

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At one time or another every factor known or believed to be concerned in the coagulation of blood has been declared to be deficient or inoperative in haemophilia. From this mass of contradictory statements it is impossible to extract more than a very few which may be regarded as well established, and still fewer which are without doubt. Much of the obscurity, doubtless, is due to the unsatisfactory nature of our knowledge of the mechanism of blood coagulation, concerning which two main and several subsidiary hypotheses appear to be warring for supremacy, while confusion has been worse confounded by the wholesale introduction of synonyms—in many cases descriptive of merely hypothetical substances.

It becomes necessary, therefore, to preface any discussion of the causation of haemophilia by a glossary of the terms employed and by a brief account of the particular hypothesis of blood coagulation to which the authors adhere. Further, if the discussion is to be of any value, it is imperative to limit the terms employed to the minimum, and, as far as is possible, to found all deductions on those parts only of the mechanism of coagulation concerning which there is reasonable unanimity of opinion.

The nomenclature and hypothesis of coagulation adopted in this paper are essentially those of Morawitz (1).

Fibrinogen, present in unshed blood, is converted to *fibrin* by the action of *thrombin*. Thrombin is not present in unshed blood, but is formed from pre-existing *prothrombin* by the combined action of *calcium salts* and *thromboplastic substance*. We prefer to use this last term in preference to that employed by Morawitz himself—*thrombokinas*e—since doubt has been cast on the idea that the substance functions as an enzyme. Indeed, the term we have adopted, though less committal than that of Morawitz, is itself unsatisfactory, for the factor it connotes may be a condition rather than a substance. However, we have employed it in preference to introducing a new term.

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It is thoroughly established that fibrinogen is a globin occurring in the blood-plasma; the distribution of prothrombin, however, is not so clear. Melanby (2) describes it as being in close association with fibrinogen, and his evidence is accepted—apparently without further examination—by Pickering (3). On the other hand, a number of workers claim that only very small amounts of prothrombin are present in the circulating plasma, and that the greater part of that required in coagulation is liberated, when the blood is shed, from the platelets, and, to a lesser extent, from the leucocytes (10, 11, 12, 13, 14).

Thromboplastic substance must be absent from the circulating plasma, as, were it present in appreciable amount, it would bring about the formation of thrombin, and so cause intravascular clotting or negative phase blood, unless of course one postulates an antithrombin, as does Howell (4, 5). Many workers have claimed that plasma, completely denuded of all formed elements, is still capable of coagulation, though they admit that in these circumstances clotting is extremely slow (e. g. 6). Their results, however, do not necessarily indicate the presence of thromboplastic substance in circulating plasma. In the first place, a certain amount may have entered the plasma during its manipulation, and secondly, a catalyst is classically defined as a substance capable of accelerating a chemical reaction, though not of initiating it. Of these objections the first holds, whatever view be taken of the action of thromboplastic substance; the latter, only if one agrees with Morawitz that it is enzymic. In any case, thromboplastic substance, whatever its mode of action, appears to be necessary for the rapid clotting of blood. It is usually described as present in the cellular tissues, including the formed elements of blood, and to be found especially in such tissues as brain and testis, which are rich in phosphatides. Howell, indeed, who introduced the name we employ, *thromboplastic* substance, identifies it with kephalin, and believes its action to consist in the neutralization of an antiprothrombin which he terms *heparin* and considers to be also a phosphatide.

It appears, then, that whatever the mechanism by which thrombin is formed, the velocity of the reaction will be increased by any means which will accelerate the pouring of prothrombin and thromboplastic substance into the plasma. It is well known, for example, that blood clots more rapidly if it is allowed to flow over a bruised tissue surface—an effect especially noticeable in avian blood, whereby it receives additional thromboplastic substance. Similarly, acceleration of clotting has frequently been observed when lysis or switching has destroyed the cellular elements.

In this connexion, some experiments of our own yielded interesting results. Firstly, we studied the relation between the coagulation time and the amount of lysis. For this purpose haemophilic blood was used, since the greatly increased coagulation time facilitated manipulation and allowed a number of observations to be made on each sample. Blood was drawn by venepuncture, using a short wide-bore paraffined needle. 2 c.c. were added to each of a series of test-tubes placed in a water-bath at 38° C., and containing quantities of distilled water varying from 0.0 to 3.0 c.c. The contents of each test-tube were rapidly mixed,

and the time of coagulation taken, the blood being considered to have clotted when the test-tube could be inverted safely. Table I shows the results of typical experiments. In every case the time of coagulation decreased with the addition of water, reaching a minimum when complete lysis was attained. Further addition of water lengthened the coagulation time, an effect which was probably one of mere dilution. At the optimum, a reduction of 60 per cent. in the coagulation time was attained.

Next, again using haemophilic blood, we investigated the effect of switching with a bundle of fine wires. In this series our first aim was to ascertain the amount of switching required to produce the optimum effect, for, with the quantity of blood usually available, it was not possible to carry out a variety of experiments on each sample. The time of coagulation decreased as the time of switching increased up to about two minutes, and remained roughly constant up to four minutes; thereafter defibrination became appreciable and the coagulation time again increased. A number of experiments on different samples then showed that two minutes' switching of the blood was capable of reducing the coagulation time by about the same amount as was complete lysis, i.e. 60 per cent. (Table II).

Turning then to normal blood, we investigated the effect on the coagulation time of two minutes' switching, and of lysis by the same amount of distilled water as was employed for haemophilic blood. (Since the fragility of haemophilic corpuscles determined by the method described by Beaumont and Dodds (7) had been found to be normal, it was assumed that the optima for the two series would coincide.) To our surprise we found that, whereas switching produced an acceleration of clotting comparable with that obtained in haemophilic blood, lysis lowered the coagulation time very slightly (Table III).

The bearing of these experiments on the causation of haemophilia will be discussed later; at present it is intended to consider only their implications with respect to the process of coagulation. Lysis, under the experimental conditions, destroyed, at any rate, almost all the formed elements of the blood, for Minot and Lee (8) have found that the platelets are largely destroyed when the tonicity is reduced to such an extent as to cause almost complete lysis of the erythrocytes. Hence in our experiments there must have been liberated a large amount of the prothrombin, and also any thromboplastic substance existing in the cells. In switching, cell destruction did not take place to anything like the same extent, yet a much greater acceleration of clotting was produced. Whilst it is obvious that much further work is necessary before an adequate explanation of this phenomenon can be given, we would suggest tentatively that it affords an indication of the non-existence of preformed thromboplastic substance. It may be that it is formed in the break-down of cells in contact with air or certain surfaces, but that when the cells are suddenly disintegrated, as in lysis, only some of the precursor substances are able to react in the normal way. On this view, switching, by increasing the break-down (in the normal way) of the cells, would increase the supply of thromboplastic substance and so accelerate coagulation; lysis, by pre-

venting the formation of much of the thromboplastic substance, would have little or no accelerating action.

As regards the mode of interaction of the various participants, we are not prepared to be so definite as was Morawitz. Thus he named thrombokinas with the idea that it is an enzyme, a question on which, in view of later work dealing especially with the quantitative nature of its action, we prefer to keep an open mind. A knowledge of its exact mode of action does not as yet appear to be essential to our work. The work of Rettger (9) and others appears to indicate a definite quantitative relationship between the amount of thrombin and the amount of fibrin produced. Taken in conjunction with the observation that an amount of thrombin below a certain limit can never produce complete coagulation, this would indicate that thrombin, at any rate, does not function as an enzyme, but forms a compound or complex with the fibrinogen.

Turning now to the more particular question of the abnormalities discoverable in haemophilia, we may first review briefly some of the suggestions which have been advanced by previous workers.

In the first place, it must be emphasized that the evidence points strongly to the conclusion that the slowing of coagulation in haemophilia occurs prior to the formation of thrombin. Wöhlisch (15) has shown that the fibrinogen is normal both in behaviour and amount. Addis (16, 17) and others (8, 15, 18), too, have found that haemophilic blood is clotted as readily by thrombin as is normal blood, and that the thrombin of haemophilic blood and that of normal blood possess equal coagulating power. Hence the fibrinogen and thrombin of haemophilic blood are deficient neither in quantity nor in quality.

There remain, then, three possibilities. The defect may be due to a deficiency (qualitative or quantitative) in the calcium, the thromboplastic substance, or the prothrombin.

Wright has claimed that a deficiency of calcium is a cause of haemophilia. It has, however, frequently been found, as by the present authors (Table IX), that the calcium content of haemophilic serum is within the normal range, and that addition of calcium salts does not cause any acceleration of clotting. Further, in such diseases as tetania parathyreopriva, where the blood calcium is much lowered, there is no corresponding increase in the coagulation time.

A shortage of thromboplastic substance has been suggested by Sahli (19) as the cause of the delayed clotting in haemophilia, and this suggestion has been supported by Morawitz and Lossen (20), while Nolf and Herry (21) consider the thromboplastic substance to be altered in quality rather than in quantity. Addis (16), however, has concluded that there is deficiency of thromboplastic substance neither in the formed elements of the blood nor in the body tissues.

It would seem, then, that the defect lies in the prothrombin, and various investigators (22, 23, 24) have stated that in haemophilic blood this substance is present in smaller amounts than in normal blood. The consensus of opinion, however, appears to be (e.g. 8, 15, 17) that the defect is qualitative rather than

quantitative. It does not, however, follow that the constitution of the prothrombin is abnormal in haemophilia, though that would readily account for its slow conversion to thrombin. Indeed, the production of a normal thrombin, which has been shown to take place, would strongly indicate a normally constituted prothrombin. It seems more probable that the defect consists in an abnormally slow availability of prothrombin, as has been suggested by Macleod (25) and by Howell (26). Evidence in favour of this view is adduced from the experiments described below.

Still other hypotheses regarding the cause of haemophilia have been advanced. Thus Fiessly (27) has claimed that haemophilic plasma contains a substance which prevents the formation of prothrombin. Pickering and Gladstone (28) explain the disease on the basis of the theory of blood-clotting advanced by Pickering as due to the presence of a relative excess of a stable protective colloid.

Localization of Coagulation Defect.

Since all modern investigators are agreed that the deficiency in haemophilia does not lie in either the thrombokinase or fibrinogen, we have not thought it worth while to repeat their experiments. We have confined ourselves to a study of the circulating prothrombin and calcium, the former being generally accepted as defective, and the latter being claimed by some to be occasionally deficient.

That the thrombin activity of haemophilic serum is as great as that of normal serum has been shown by several investigators (Addis (17), Minot and Lee (8), Wöhlisch (15), Mills (18)). The importance of this observation has led us to repeat the experiments at body temperature. Table IV definitely supports the view that the thrombin content in haemophilia serum is as great as that in normal serum, since each accelerates the clotting of normal blood to the same degree. Since the amount of fibrin is known to be normal and the amount of thrombin has been shown to be normal in clotted haemophilic blood, the actual quantity of prothrombin present in the unclotted blood must be normal, since prothrombin acts quantitatively.

Having decided that any prothrombin defect was not quantitative, we proceeded to define further and isolate this defect by liberating the prothrombin from the platelets. To do this we repeated and amplified the admittedly inconclusive experiments of Minot and Lee (8). First we determined the fragility of haemophilic corpuscles by observations on their resistance to hypotonic saline solutions (Beaumont and Dodds (7)), and found this to be perfectly normal (Table VIII), thus confirming the observations of Minot and Lee. We then proceeded to determine the action of lysis. Table I shows the effect of varying degrees of lysis on the coagulability of haemophilic blood. As has been explained, the greatest reduction in the coagulation time was at that point where lysis was complete, with a minimal amount of dilution. Tables II, III, and VII show the effects of this lysis at the optimum dilution in normal as compared with haemophilic blood. The difference is very striking in that whereas lysis of haemophilic

blood produces a 60 per cent. decrease in the coagulation time, lysis of normal blood produces only a 7 per cent. decrease. Two factors, however, must be excluded before any conclusion can be reached. First, we have broken up not only the platelets but also the corpuscles. To exclude the latter as being responsible for the decrease, a platelet suspension in plasma was prepared according to the method described by Bayne-Jones (14), the presence of platelets being demonstrated microscopically. Tables V, VI, and VII show almost the same degree of difference between the decrease of coagulation time in lysed normal and lysed haemophilic platelet suspension as was found with whole blood.

The other factor which must be excluded is that not only the prothrombin, but also a small amount of thromboplastic substance, is liberated by the lysis of platelets (Austin and Pepper (12), Bayne-Jones (14), Morawitz (11), Howell (13)). To exclude the possibility of this thromboplastic substance being responsible for the decrease, we compared the effect of switching normal and haemophilic bloods (Tables III and VII). Here, since we are bruising the cellular elements of the blood, thromboplastic substance will be liberated (12, 13, 29). The experiments showed that haemophilic and normal blood respond to almost the same degree, indicating that it is not the liberation of thromboplastic substance which is responsible for the abnormally large decrease in the coagulation time when haemophilic blood is lysed.

One may conclude that in haemophilia lysis of the platelets brings about a marked decrease in the coagulation time by liberating prothrombin. In normal blood, with a normal liberation of prothrombin, lysis brings about little, if any, acceleration of clotting.

This would indicate that the deficiency in haemophilia consists in part in a slow liberation of prothrombin from the platelets. That there is probably some further defect is clearly shown by the fact that lysis of the platelets alone does not bring the clotting time of haemophilic blood to within normal limits.

The Acid-base Balance of the Blood.

Investigation of the acid-base balance of the blood was made in each case, and was as complete as the material and facilities at our disposal permitted. Direct determinations of hydrogen-ion concentration were unfortunately not possible.

The first observation made was a single point on the carbon dioxide dissociation curve of Case III. This fell within normal limits, and the pH, calculated by means of the Henderson-Hasselbalch (30) equation, was normal. This confirms the findings of Hurwitz and Lucas (23), and does not support the suggestion of Mellanby (2) and other authors that undue alkalinity of the blood may be a causative factor in haemophilia. Subsequent observations in this and other cases confirmed this initial finding, but in addition revealed a hitherto unsuspected abnormality. When the carbon dioxide dissociation curve of the blood of any individual is determined by the method described by Meakins and Davies (31), it has been found that the carbon dioxide combining power (percentage increase or

decrease of carbon dioxide content as compared with that of the blood of Haldane at the same carbon dioxide pressure) remains approximately the same for any carbon dioxide pressure within or even beyond the physiological range. In these haemophilic cases, however, with increasing pressures of carbon dioxide, the carbon dioxide combining power of the blood (expressed as above) diminished. In other words, there was an abnormal flattening of the carbon dioxide dissociation curve. Hence for any increase in carbon dioxide pressure the amount of bicarbonate in the blood did not increase to a normal extent, and, assuming the Henderson-Hasselbalch equation to be valid in these cases, the pH change for any given change of carbon dioxide pressure was greater than normal. That is to say the buffering mechanism of the blood in these cases was deficient.

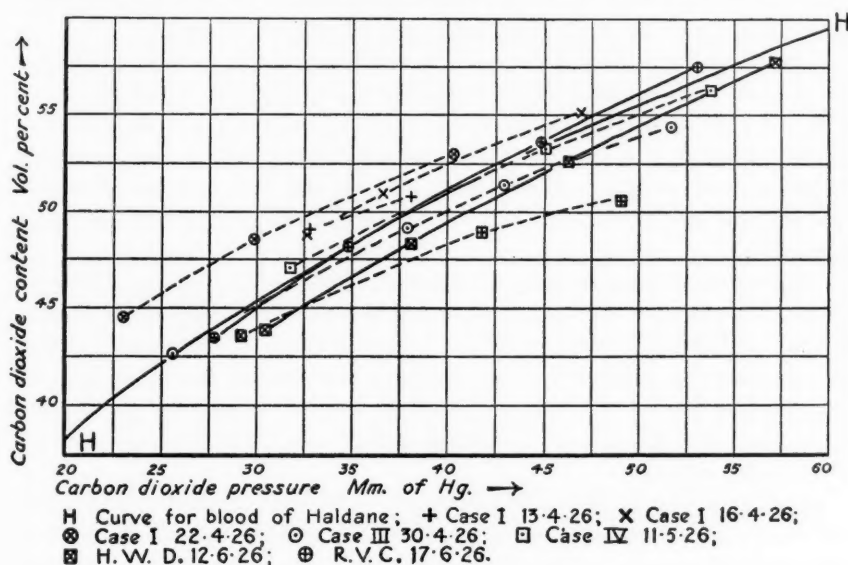


FIG. 1.

This is shown in Fig. 1 and Table VIII. The estimations of carbon dioxide content were made upon duplicate samples of 2 c.c. each by means of the Haldane blood-gas apparatus, and in the majority of cases duplicates agreed to within 0.5 vol. per cent. On each occasion the estimations were made on successive portions of a single sample of oxalated blood preserved by the addition of a trace of sodium fluoride (Lovatt Evans (32)) and in a vessel surrounded by crushed ice. It can be seen that in the cases of the two normals (H.W.D. and R.V.C.) the carbon dioxide combining power of the blood *increased* with increasing carbon dioxide pressure. In other words, the carbon dioxide dissociation curves of these two individuals were, at the physiological range, slightly steeper than that of Haldane. The flattening shown by the patients is not always marked, nor is it constant from day to day in a given case. Further work alone can show whether this variability is correlated with the variability in coagulation time which is

known to occur from day to day in haemophilia. In Case I the flattening was more marked on 13.4.26 than on 16.4.26 and 22.4.26. Similar flattening was observed in Case II on 5.6.26 (Table VIII), but the curve for this individual was not included in Fig. 1 in order to avoid undue confusion. In Case IV flattening was marked on 17.5.26, but almost absent on 21.9.26 (Figs. 1 and 3). In no case, however, was a curve steeper than that for Haldane's blood observed.

From the above findings it can be seen that the buffering mechanism of the blood in this group of cases was less efficient than in the cases of Haldane, H. W. D., and R. V. C., although it is difficult to state definitely whether this diminution of buffering power was greater than may possibly occur in a normal individual. It is significant, however, that the curves of all the patients examined were flatter than the published curve of Haldane's blood (33), while those of the two normals (determined by precisely the same technique) were slightly steeper.

The normal buffering of the blood is dependent upon a number of factors. These have been discussed in a quantitative manner by Van Slyke (34), L. J. Henderson (35), and others. The principal factors, however, are as follows: (1) The liberation of base from loose chemical combination with haemoglobin and with the plasma proteins; (2) combination of carbonic acid with portion of the base of disodium phosphate; and (3) the interchange of ions between plasma and corpuscles.

These factors were severally investigated. Estimation of haemoglobin percentage and of oxygen-combining power revealed no abnormality of the haemoglobin. Estimations of total and of non-protein nitrogen in the plasma revealed no quantitative abnormality. The phosphates were normal (see Table IX). It was therefore decided to investigate the ionic interchange between plasma and corpuscles. For this purpose methods essentially similar to those of Joffe and Poulton (36) were used.

Sufficient blood for complete investigation (200-250 c.c.) was drawn by venepuncture without stasis and with the forearm immersed in water at about 45° C. This was oxalated, and, in order to prevent glycolysis, a trace of sodium fluoride was added. The blood was then placed under paraffin in a cylindrical jar standing in a larger beaker of crushed ice. The ice was replaced as it melted. In this way blood could be kept for 12-18 hours without loss of carbon dioxide combining power. The amount of fluoride added was not sufficient to interfere with the chloride estimations, and, being added to the whole bulk of blood, was constant in each successive portion used.

For the last estimation approximately 100 c.c. of blood were placed in a 400 c.c. cylindrical saturating flask such as was used by Christiansen, Douglas, and Haldane (33). The carbon dioxide was removed as far as possible by exposing the blood to a vacuum at 37° C. for about ten minutes. Room air was then readmitted and the saturator placed in the thermostat bath for fifteen minutes, the pressure being released at the end of the first five minutes. At the end of fifteen minutes the saturating flask was removed and wrapped in warm cloths. Two 2 c.c. samples of blood were withdrawn for estimation of carbon dioxide

percentage, from which the pressure of carbon dioxide was calculated. The remainder of the blood was then run under paraffin into a centrifuge tube and rapidly centrifugalized. After 20–25 minutes' centrifugalization samples of plasma were removed from beneath the paraffin layer for duplicate estimations of carbon dioxide and chloride. The remainder of the plasma was pipetted off into a vessel

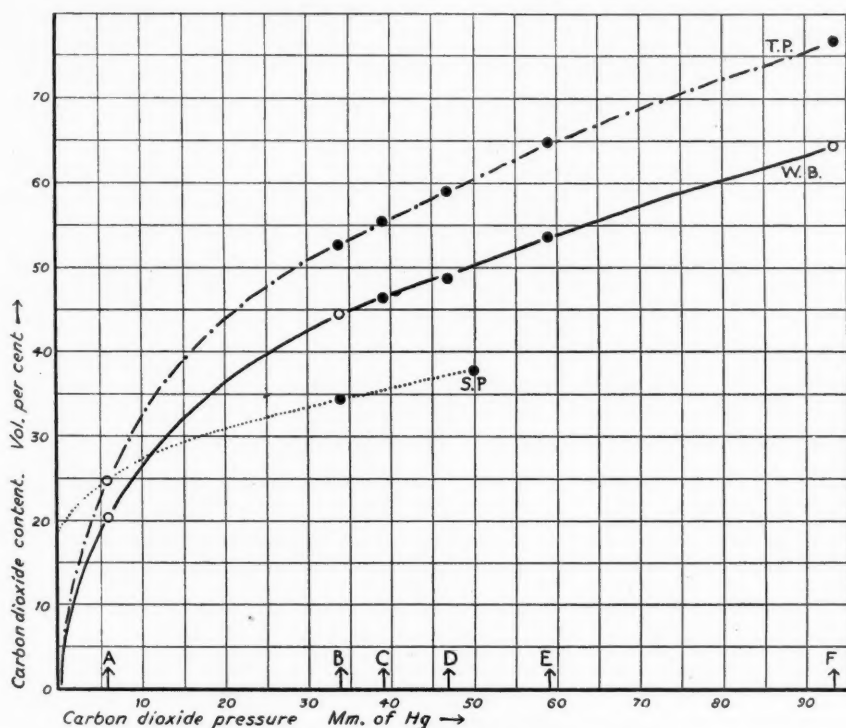


FIG. 2. Case III. 18.9.26. (See Protocol I.)

T. P. = Curve for true plasma.

W. B. = " " whole blood.

S. P. = " " separated plasma.

At A	True plasma	NaCl, 575 mg. per cent.
" B	"	" 575 " "
" C	"	" 575 " "
" D	"	" 575 " "
" E	"	" 575 " "
" F	"	" 569 " "

surrounded by ice, and successive portions of it used for the determination of the carbon dioxide combining power of separated plasma as well as for total and non-protein nitrogen.

The remaining determinations were made in similar manner, only 25 c.c. of blood being used for each point. This amount was sufficient to allow of duplicate 2 c.c. samples of whole blood being used for carbon dioxide content and duplicate determinations of chlorides and carbon dioxide on the plasma after

centrifugalization under paraffin. The chlorides were estimated by the method of Wetmore (38).

Results obtained in this manner on Cases III and IV are shown in Figs. 2 and 3 (detailed figures being given in Protocols I and II). The investigation revealed the surprising finding that no alteration of plasma chloride occurred at

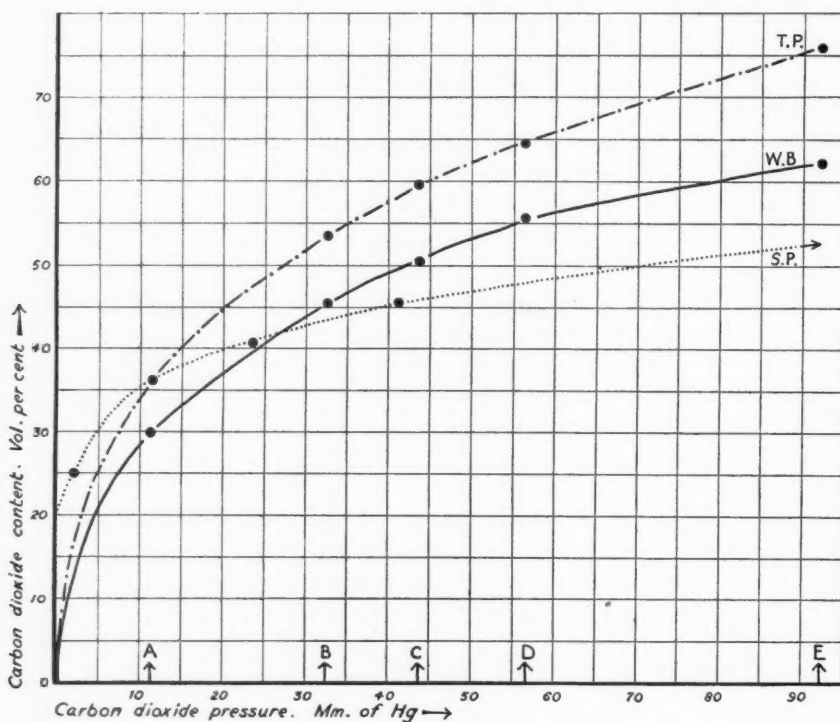


FIG. 3. Case IV. 21.9.26. (See Protocol II.)

T. P. = Curve for true plasma.
 W. B. = " " whole blood.
 S. P. = " " separated plasma.

At A	True plasma NaCl, 544 mg. per cent.
" B	" " " 538 " "
" C	" " " 538 " "
" D	" " " 538 " "
" E	" " " 538 " "

different carbon dioxide pressures, except to a very slight extent at extreme ranges of pressure. From the data of L. J. Henderson (35) it can be seen that if in fully oxygenated blood the carbon dioxide pressure changes from 40 mm. to 50 mm. the plasma chloride concentration changes from 99.5 to 98.6 mm. per litre (from 577 to 572 mg. per cent.). Similarly, for large variations in carbon dioxide pressure, Dautrebande and Davies (38) found more considerable alterations in plasma chloride concentration. Thus in the blood of H. W. D., when the

carbon dioxide pressure was changed from 42.5 to 143.3 mm., the plasma chlorides changed from 662 to 587 mg. per cent. and in L. D. a pressure change from 6.8 to 195 mm. was associated with a chloride change from 663 to 600 mg. per cent. Since it is in the form of hydrochloric acid that chlorine passes into the corpuscles with increasing carbon dioxide pressures, there remains in the plasma a larger amount of available base (mainly sodium) for combination with the increasing amount of carbon dioxide. The extent of this increased carbon dioxide carrying power of the plasma brought about by ionic interchange between cells and plasma is shown by the difference in slope of the curves for true plasma and separated plasma in the results of Joffe and Poulton (36). Van Slyke and Cullen (39) found that the chlorine transfer from plasma to corpuscles was sufficient to account for 72 per cent. of the alkali increase in the plasma when the carbon dioxide pressure of the blood was raised from 29 to 53 mm. In our results (Figs. 2 and 3) the increased amount of alkali in the true plasma, with increasing carbon dioxide pressures, was practically the same as in the results of Joffe and Poulton (36), yet, as we have shown, this is not due to transference of chlorine, or, by analogy, of other anions present in smaller amounts. It must therefore be due to transference of kations (principally K^+ and Na^+) in the opposite direction, a phenomenon which Hamburger (40) showed to occur normally, but the effect of which Van Slyke (34) calculated to be only slight as compared with that of the anion transfer.

From the above considerations it can be seen that it is our third factor (ionic interchange between corpuscles and plasma) in the buffering mechanisms of the blood which is abnormal in these cases of haemophilia. The normal chloride shift does not occur, except to a very slight extent, with extreme variations of carbon dioxide pressure, but the deficiency seems to be compensated for almost completely by some other mechanism which, so far as we can see, can only be an interchange of kations in the opposite direction. So that we may say that in these haemophilic cases there is an alteration in the permeability of the cell-walls of the red corpuscles, that anions pass through much less readily than normally, while kations pass through more readily. Another hypothesis might be advanced and is worthy of investigation, namely, the possibility of a *qualitative* change in plasma proteins and a consequent alteration of the Donnan membrane equilibrium between cells and plasma.

Much more work needs to be done before the precise significance of these abnormalities can be determined. Yet it seems highly significant that in these haemophilic cases there is an alteration in the carbon dioxide carrying mechanism of the blood as well as a clotting defect, largely due, as shown above, to slow liberation of prothrombin, both of which may be explained by an alteration of cell permeability.

Summary and Conclusions.

1. From a study of the effects of lysis and switching on the coagulation of normal blood we have advanced, tentatively, the suggestion that thromboplastic substance does not exist as such in unshed blood.

2. From an extension of this study to haemophilic blood and to haemophilic plasma containing platelets we have reached the conclusion that in part the coagulative defect in haemophilic bloods consists in a slow liberation of prothrombin from the platelets.

3. In haemophilic blood the serum calcium, the plasma non-protein nitrogen, total nitrogen and chlorides, and the blood cholesterol and inorganic phosphorus are present in normal amounts.

4. In haemophilia there is a further coagulative defect, namely, the slow conversion of prothrombin into thrombin. The thrombin, when formed, is normal in amount.

5. Study of the acid-base balance in haemophilia showed that the pH of the arterial blood, calculated from the Henderson-Hasselbalch equation, is within normal limits. The CO₂ dissociation curves of all cases showed, at the physiological range, an undue flattening as compared with curves of the blood of Haldane and other normal individuals (determined by similar methods). It was shown that the normal chlorine interchange between corpuscles and plasma with varying CO₂ pressures occurred only to a very slight extent and with extreme variations of pressure.

6. It is suggested that the slow liberation of prothrombin and the deficient chlorine interchange may be due to a common cause.

Our thanks are due to Professor G. Lovell Gulland, without whose assistance it would have been impossible to collect such an extensive series of cases. We also desire to thank the patients themselves for their willing co-operation and readiness to submit to the withdrawal of large quantities of blood and other procedures, knowing them to be of non-therapeutic nature. Dr. H. Bogle was good enough to carry out several determinations of cholesterol.

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TABLE I.

Effect of Lysis on the Coagulation Time of Haemophilic Blood.

Temperature 37° C.

Vol. of Water added to 2 c.c. Blood.	Extent of Lysis.	Coagulation Time in Min.	
		Case IV.	Case V.
c.c.			
0	None	45	60
0.25	None	43	44
0.50	Partial	23	27
1.00	Partial	23	20
1.50	Complete	20	19
2.00	Complete	20	19
3.00	Complete	38	33
0	None	46	59

TABLE II.

*Effect of Lysis and Switching on the Coagulation Time of Haemophilic Blood.**Lysis:* 1.5 c.c. distilled water added to 2.0 c.c. blood.*Switching:* Blood switched for two minutes with bundle of fine wire.

Temperature 37° C.

Case.	Coagulation Time in Minutes.		
	Normal.	With Lysis.	With Switching.
I	35	14	13
I	46	21	23
I	34	15	24
I	60	25	8
III	38	14	15
IV	45	20	18
V	60	19	23
V	50	25	—

Average decrease in coagulation time after lysis, approx. 60 per cent.

Average decrease in coagulation time after switching, approx. 60 per cent.

TABLE III.

Effect of Lysis and Switching on the Coagulation Time of Normal Blood.

Case I, 37° C.; all others, 18° C.

Lysis: 1.5 c.c. distilled water added to 2.0 c.c. blood.*Switching:* Blood switched for two minutes with bundle of fine wire.

Case.	Coagulation Time in Minutes.		
	Normal.	With Lysis.	With Switching.
I	6	5	4
II	14	14	9
III	13	11	9
IV	13	10	5
V	14	14	6
VI	10½	11	5
VII	14	13	9
VIII	12	12	5½
IX	17	15	10
X	15	14	—

Average decrease in coagulation time after lysis, approx. 7 per cent.

Average decrease in coagulation time after switching, approx. 45 per cent.

Note.—In Tables I and III the time of coagulation is taken from the time of withdrawal of the blood, and thus includes the two minutes of switching.

TABLE IV.

Clotting Power of Haemophilic as compared with Normal Serum.

Temperature 37° C.

1 c.c. serum added to 2 c.c. blood (haemophilic) sera used in any one experiment were of the same age and never more than 30 hours old.

Case.	Coagulation Time in Minutes.		
	Control.	With Normal Serum.	With Haemophilic Serum.
I	35	5	5
I	46½	11	11½
I	35	11½	14
VI	60	144	14

TABLE V.

Effect of Lysis on the Coagulation Time of Re-calcified Normal Plasma.

The blood was oxalated with 1 c.c. of 1 per cent. sodium oxalate in 0.9 per cent. sodium chloride per 8 c.c. of blood. The plasma was separated after centrifugalizing for 15 minutes at 1,000 revs. per minute. 2 c.c. plasma were added to 1 c.c. of 0.5 per cent. CaCl_2 + 1.5 c.c. distilled water. Coagulation was allowed to take place at room temperature. Control: 2 c.c. plasma + 1 c.c. 0.5 per cent. CaCl_2 .

Case.	Coagulation Time in Minutes.	
	Control.	With Lysis.
I	20	17
II	11	10
III	26	21
IV	12	10½
V	13	12½
VI	17	15

Average decrease in coagulation time after lysis, 13 per cent.

TABLE VI.

Effect of Lysis on Coagulation Time of Re-calcified Haemophilic Plasma.

Technique as detailed in Table V.

Case.	Coagulation Time in Minutes.	
	Control.	With Lysis.
V	186	104
V	154	91
V	251	115
V	148	107
VI	220	140

Average decrease in coagulation time after lysis, 42 per cent.

TABLE VII.

Summary.

	Per cent. Decrease in Coagulation Time.	
	Normal.	Haemophilic.
Lysis of whole blood	7	60
Lysis of re-calcified plasma	13	42
Switching of whole blood	45	60

TABLE VIII.

CO₂-combining power at different CO₂ pressures for Cases I-IV and for two normals.
Further figures for Cases III and IV are given in Protocols I and II.

Case No.	Date.	CO ₂ Pressure mm. of Hg.	CO ₂ Content. Vol. per cent.	CO ₂ -combining Power per cent.	CO ₂ Content of Initial Venous Blood. Vol. per cent.
Normal	12.6.26	30.4	43.8	-3.9	—
		38.0	48.4	-3.2	—
H. W. D.	"	46.2	52.6	-2.4	—
		57.2	57.7	-1.7	—
Normal	17.6.26	27.7	43.5	-0.9	—
		34.7	48.2	± 0.0	—
R. V. C.	"	44.8	53.6	+0.6	—
		53.0	57.5	+1.2	—
III	9.4.26	33.7	49.3	—	—
	30.4.26	25.5	42.6	+0.5	52.6
		37.8	49.1	-1.6	—
		42.9	51.4	-1.9	—
		51.5	54.2	-3.5	—
		51.6	54.3	-3.5	—
I	13.4.26	32.7	49.1	+4.5	48.7
		38.0	50.8	+1.6	—
	16.4.26	32.6	48.7	+3.8	—
		36.5	50.9	+3.5	—
		46.9	55.1	+1.7	—
	22.4.26	23.0	44.6	+9.6	—
		29.9	48.5	+7.1	—
		40.2	52.9	+3.5	—
IV	6.5.26	26.8	43.1	-0.5	52.3
		42.8	52.3	-0.2	—
		50.5	54.2	-2.9	—
	11.5.26	31.7	47.1	+1.5	52.0
		45.0	53.2	-0.2	—
		49.7	54.5	-1.8	—
		53.7	56.3	-1.4	—
	17.5.26	29.2	43.7	-2.5	—
		49.0	50.6	-8.2	—
II	5.6.26	33.2	49.6	+4.9	52.1
		43.9	54.8	+3.6	—
		53.6	58.6	+2.6	—

TABLE IX.

Concentration of Various Constituents in Haemophilic Blood.

Calcium estimated by the method of Kramer and Tisdall (42); diffusible calcium by filtration through collodium; phosphorus by the method of Stewart and Archibald (43); nitrogen by micro-kjeldahl on whole plasma or Folin-Wu filtrate; chlorides by the method of Wetmore (38); cholesterol by the method of Bloor (44).

Case.	Serum Ca. Mg./100 c.c.		Blood Phosphorus. Mg./100 c.c.		Plasma Nitrogen. Mg./100 c.c.		Blood Chole- sterol. Mg./100 c.c.	Plasma Chlorides. Mg. NaCl/ 100 c.c.
	Total.	Diffu- sible.	In- organic.	Total Acid Soluble.	Non- protein.	Total.		
I	9.9	6.0	4.90	—	29	1240	—	—
II	9.7	5.6	4.73	27.35	34	1280	—	587
III	9.7	5.8	2.65	—	32	1160	169	575
IV	9.5	—	2.35	—	40	1320	—	538
V	10.1	—	4.76	—	40	1250	154	—
VI	9.6	5.8	3.10	—	36	1205	172	—

Appendix I, Case Reports.

Case I. W.E., aged 25. Male. *Family history.* Definite of haemophilia for one generation (previous family history unknown); four definite, four indefinite (died in infancy) cases in family. *Symptoms.* Bruises easily. Typical haemorrhages into joints, bowel, kidneys, gums, and nose. Almost fatal haemorrhage from scalp wound. Joints typically ankylosed. Blood coagulated at 37° C. in 46 mins.

Case II. J.C., aged 20. Male. *Family history.* Definite of haemophilia for one generation only. Three haemophilic brothers; one haemophilic cousin. *Symptoms.* Bruises easily. Frequent epistaxis and bleeding from gums, sometimes leading to severe anaemia. Very severe haemorrhage from trauma on three occasions, once almost fatal. No haemorrhage into joints. Blood coagulated at 37° C. in 23 min.

Case III. J.W.S., aged 41. Male. *Family history.* Definite of haemophilia for five generations. Twelve cases on record. *Symptoms.* Bruises easily. Typical haemorrhage into joints, kidneys, bowel, gums, and nose. Many trivial accidents, followed by severe haemorrhage. Blood coagulated at 37° C. in 38 min.

Case IV. J.C., aged 25. Male. *Family history.* First cousin of patient I. *Symptoms.* Bruises easily. Typical haemorrhage into joints, gums, and nose. Very severe haemorrhage from trauma on four occasions, once almost fatal. Blood coagulated at 37° C. in 56 min.

Case V. F.J.D., aged 34. Male. *Family history.* Definite of haemophilia for three generations. Six cases in family. *Symptoms.* Bruises easily. Typical haemorrhage into joints, kidneys, lungs, gums, and nose. One almost fatal haemorrhage after accident. Blood coagulated at 37° C. in 60 min.

Case VI. J.McD., aged 40. Male. *Family history.* First cousin of patient III. *Symptoms.* Bruises easily. Typical haemorrhage into joints, kidneys, and gums. Numerous severe haemorrhages after trauma. Blood coagulated at 37° C. in 65 min.

*Appendix II, Protocols.**Protocol I. Case III. 18.9.26. (See Fig. 2.)*

Venous blood drawn without stasis (forearm immersed in hot water). Oxalate and fluoride added. Blood kept in vessel under paraffin and surrounded by ice.

At 93.2 mm. carbon dioxide pressure.

CO₂ content of whole blood 64.2 vol. per cent.

" " true plasma 76.5 vol. per cent.

Chlorides (as NaCl) in true plasma 569 mg. per cent.

CO₂-combining power
— 9.6 per cent.

At 58.6 mm. carbon dioxide pressure.

CO₂ content of whole blood 53.2 vol. per cent.

" " true plasma 64.8 vol. per cent.

Chlorides (as NaCl) in true plasma 575 mg. per cent.

CO₂-combining power
— 10.3 per cent.

At 46.7 mm. carbon dioxide pressure.

CO₂ content of whole blood 48.8 vol. per cent.

" " true plasma 59.0 vol. per cent.

Chlorides (as NaCl) in true plasma 575 mg. per cent.

CO₂-combining power
— 9.8 per cent.

At 38.9 mm. carbon dioxide pressure.

CO₂ content of whole blood 46.7 vol. per cent.

" " true plasma 55.6 vol. per cent.

Chlorides (as NaCl) in true plasma 575 mg. per cent.

CO₂-combining power
— 7.3 per cent.

At 33.7 mm. carbon dioxide pressure.

CO₂ content of whole blood 44.3 vol. per cent.

CO₂-combining power
-6.9 per cent.

" " true plasma 52.7 vol. per cent.

Chlorides (as NaCl) in true plasma 575 mg. per cent.

At 5.8 mm. carbon dioxide pressure.

CO₂ content of whole blood 20.4 vol. per cent.

CO₂-combining power
-7.3 per cent.

" " true plasma 24.7 vol. per cent.

Chlorides (as NaCl) in true plasma 575 mg. per cent.

The plasma remaining from this determination was used as 'separated plasma'.

Separated plasma.

Non-protein nitrogen 32 mg. per cent.

Total nitrogen 1,160 mg. per cent.

At 33.9 mm. CO₂ pressure separated plasma took up 34.7 vol. per cent. of CO₂.

" 49.9 " " " 37.8 " "

Protocol II. Case IV. 21.9.26. (See Fig. 3.)

Venous blood drawn without stasis (forearm immersed in hot water). Oxalate and fluoride added. Blood kept in vessel under paraffin and surrounded by ice.

Clotting time in test-tube at 37° C. was 55 min.

At 92.1 mm. carbon dioxide pressure.

CO₂ content of whole blood 62.1 vol. per cent.

CO₂-combining power

" " true plasma 75.8 vol. per cent.

Chlorides (as NaCl) in true plasma 538 mg. per cent.

At 56.4 mm. carbon dioxide pressure.

CO₂ content of whole blood 55.6 vol. per cent.

CO₂-combining power

" " true plasma 64.6 vol. per cent.

Chlorides (as NaCl) in true plasma 538 mg. per cent.

At 43.6 mm. carbon dioxide pressure.

CO₂ content of whole blood 50.4 vol. per cent.

CO₂-combining power
-4.4 per cent.

" " true plasma 59.9 vol. per cent.

Chlorides (as NaCl) in true plasma 538 mg. per cent.

At 32.4 mm. carbon dioxide pressure.

CO₂ content of whole blood 45.3 vol. per cent.

CO₂-combining power
-3.2 per cent.

" " true plasma 53.3 vol. per cent.

Chlorides (as NaCl) in true plasma 538 mg. per cent.

At 11.4 mm. carbon dioxide pressure.

CO₂ content of whole blood 29.8 vol. per cent.

CO₂-combining power
-0.6 per cent.

" " in true plasma 36.1 vol. per cent.

Chlorides (as NaCl) in true plasma 544 mg. per cent.

The plasma remaining from this determination was used as 'separated plasma'.

Separated plasma.

Non-protein nitrogen 34 mg. per cent.

Total nitrogen 1,320 mg. per cent.

At 2.05 mm. CO₂ pressure separated plasma took up 24.8 vol. per cent. of CO₂.

23.5 " " " 40.6 " "

40.9 " " " 45.3 " "

113.2 " " " 56.4 " "

STUDIES IN BLOOD COAGULATION AND HAEMOPHILIA¹

III. THE TREATMENT OF HAEMOPHILIA

BY RONALD V. CHRISTIE AND G. LOVELL GULLAND

(From the Department of Medicine in the University of Edinburgh)

BEFORE discussing the treatment of haemophilia, it may be as well to give a brief summary of what is known of its cause. Almost all the coagulative elements of the blood have been blamed and subsequently exonerated. Thus Sahli (1), Morawitz and Lossen (2), and Nolf and Herry (3) claimed to have proved a deficiency of thromboplastic substance (thrombokinase), Wright a deficiency of calcium, and Weil and Feissly (4) an excess of antithrombin, but all these theories have in turn been disproved. With the exception of Pickering and Gladstone (5, 6), who ascribe it to an excess of protective colloid in the prothrombin-fibrinogen complex, all modern investigators agree that the deficiency lies in the circulating prothrombin, whether it be quantitative (Howell (7), Hurwitz and Lucas (8), Klinger (9)) or qualitative (Addis (10), Sajous (11), Wöhlisch (12), Minot and Lee (13), Christie, Davies, and Stewart (14), and others). The latter (a qualitative deficiency) is the view now held by most authorities, a slow availability of prothrombin being the more or less accepted theory as to the cause of haemophilia (Macleod (15), Howell (7), Minot and Lee (13), Christie, Davies, and Stewart (14)).

Accepting a prothrombin deficiency as the causal factor, the various lines of treatment naturally fall into three groups:

- (1) The introduction of normal prothrombin from some foreign source.
- (2) The introduction of any of the other coagulative elements, thus increasing the coagulability by the law of mass action.
- (3) The introduction of some foreign substance in the hope of stimulating more rapid coagulation.

The various methods of treatment will be dealt with under these headings.

Since it is typical of the disease that the coagulability of the blood and the severity of the symptoms vary from day to day, it is essential that clinical observations should be made over prolonged periods. So many extraneous factors influence the appearance of symptoms, that these can only be taken as an approximate index of progress, unless some artificial form of trauma be applied, such as the extraction of teeth. Observations on the coagulability of the blood

¹ Received April 26, 1927.

remain as the most sound method of judging progress. As one of us has shown (16), the most accurate method of gauging this coagulability is by means of the coagulation curve. Here the coagulability of successive drops of blood from the same puncture is taken according to the method described by Gibbs (17), the results being plotted in a curve. Thus an index is obtained, not only of the coagulability of the blood, but also of the tissue reaction and platelet reaction, certainly the first, and probably the last, being deficient in haemophilia (Macleod (15), Christie (16)).

BLOOD TRANSFUSION—DIRECT METHOD.

Amount—725 c.c.

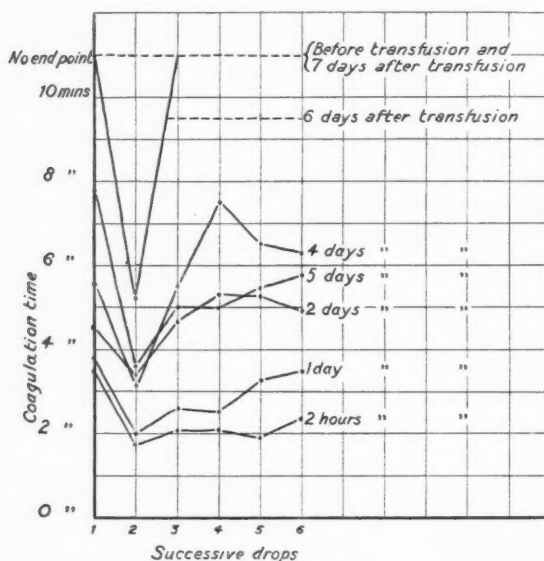


FIG. 1 (Case I).

1. Introduction of Normal Prothrombin.

(a) *Blood transfusion by direct method.* This is probably the earliest method described by which haemorrhage in haemophilia can be successfully controlled. Here we have introduced into the blood-stream a certain quantity of normal prothrombin which will act quantitatively in reducing the coagulation time. Fig. 1 shows the effect of transfusing a severe haemophilic (Case I) with 725 c.c. of normal blood. As will be seen, there was a very marked decrease in the coagulation time and lowering of the whole curve immediately after the transfusion, but this was followed by a steady rise till by the end of seven days his blood had resumed its former degree of coagulative deficiency.

(b) *Blood transfusion by citration method.* Here again prothrombin is being introduced into the blood-stream in conjunction with a certain quantity of sodium

BLOOD TRANSFUSION—CITRATION METHOD.

Amount—560 c.c.

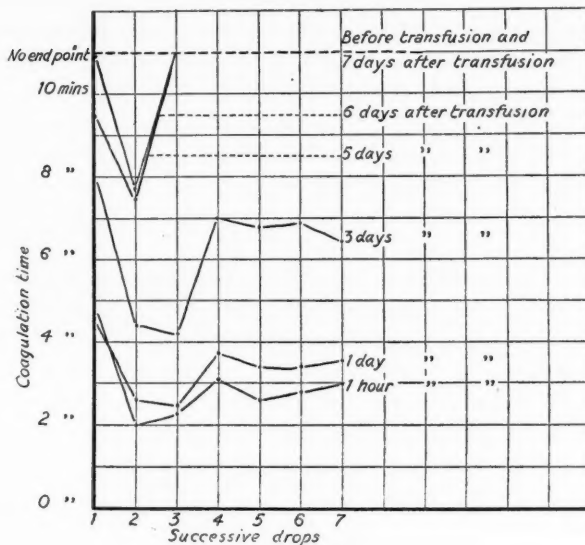


FIG. 2 (Case I).

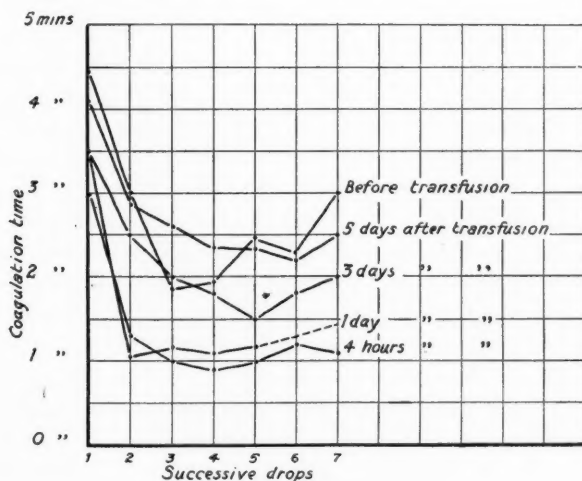


FIG. 3 (Case II).

citrate. That the amount of sodium citrate used (1.8 gm.) does not detract from the benefit of the transfusion is clearly shown by comparing Figs. 2, 3, and 4 with Fig. 1. This is only to be expected, since it has been proved beyond doubt that the calcium content in haemophilic blood is normal, and it is an accepted fact that a citrated transfusion does not decrease the coagulability of a normal recipient's blood. The possibility of there being any therapeutic value in the sodium citrate will be discussed later.

It will be seen by studying the coagulation curves (Figs. 2, 3, 4) of the four occasions on which a transfusion of citrated blood was carried out, that, as with direct blood transfusion, the improvement was transient, lasting from five to seven days. We found no subsequent increase of the coagulation time, as was suggested by Addis.

Case II is of special interest, in that the haemorrhagic tendency closely followed the changes in the coagulation curve after transfusion, extraneous influences having been reduced to a minimum. In this case a molar tooth was extracted after prolonged serum treatment. Steady haemorrhage continued from the tooth socket for eleven days after extraction, the haemoglobin dropping from 105 per cent. to 40 per cent. The patient was then transfused (Fig. 3). All haemorrhage had stopped ten minutes after its completion, and did not recur.

It will be seen from the results of these transfusions that the beneficial effect lasts from five to seven days. That the prothrombin introduced remains active for this period of time, although the blood-platelets have been shown to survive only three to four days (Duke (18, 19)), is readily explained by the work of Morawitz (20), Bayne-Jones (21), Austin and Pepper (22), Hess (23), and others, who have shown that on disintegration the prothrombin from the platelets passes into solution in the blood, and is still available for coagulative purposes.

(c) *Transfusion of defibrinated blood.* Here we are introducing a suspension of the cellular elements of the blood in serum, the active ingredient of which will be almost pure thrombin (Mellanby (24)). We have no practical experience of this line of treatment, and can only quote the work of Minot and Lee (Sajous (11)), who have shown that there is a very definite but transient improvement in the coagulability of the blood after a transfusion of 600 c.c. of defibrinated blood. This improvement had almost disappeared by the end of five days, which is very similar to what we have found in citrated and whole blood transfusion. Since there must have been a very much smaller quantity of prothrombin (in the form of thrombin) present in the defibrinated blood used by Minot and Lee, than in the whole blood and citrated blood used by us, we would suggest that it is the degree of improvement, and not the duration of improvement, that depends on the quantity of prothrombin introduced. Thus, although in Fig. 1 30 per cent. more blood was used than in Fig. 2, the duration of improvement was similar, and in Fig. 4 there was no cumulative action with regard to duration after two transfusions.

(d) *Intravenous fresh human serum.* The serum used was obtained by centrifugalizing normal blood which had been collected by venepuncture and

BLOOD TRANSFUSION—CITRATION METHOD.

Amount—560 c.c. in each.

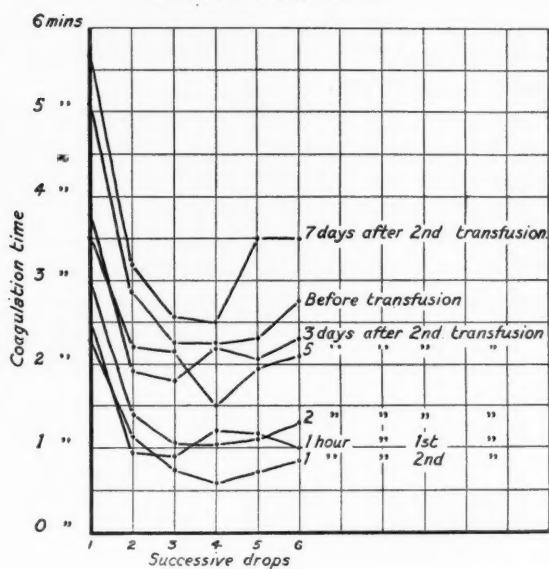


FIG. 4 (Case II).

INTRAVENOUS FRESH HUMAN SERUM.

Amount—6.2 c.c. (av.).

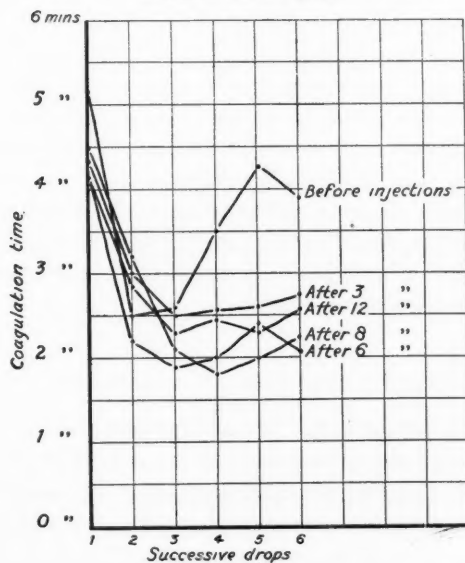


FIG. 5 (Case II).

allowed to clot. As with defibrinated blood, the serum would be poor in prothrombin content but rich in thrombin (Mellanby (24)). In no case was the more than six hours after preparation. This is well within the limits of safety, since it has been shown that serum retains its thrombin activity for three to four days (Weymouth (25), and others).

Fig. 5 shows the effect of twelve intravenous injections of fresh human serum (average quantity 6.2 c.c.), at intervals of forty-eight hours, in Case II. As can be seen, the improvement was only slight, and reached its maximum after the third injection, thereafter remaining stationary. After the last injection a carious molar tooth was extracted. That the improvement must have been only slight was shown by the haemorrhage that took place from the socket, this being controlled only by the blood transfusion (Fig. 3) already described.

These results, although roughly agreeing with what was found by Howell (7) and Addis (26), by no means support the optimistic views of Émile Weil (27, 28) and Sajous (11).

We have not attempted to reinject the patient's own serum after clotting has taken place, but can see no reason why this should not be just as efficacious as serum from normal blood, since it has been conclusively shown that the thrombin content is the same in quantity and quality (Addis (10), Minot and Lee (13), Christie, Davies, and Stewart (14)).

(e) *Introduction of sheep-serum.* On only one case (Case I) did we try the effect of this form of treatment. Unfortunately no coagulation curves could be obtained, but the coagulation time by Dale and Laidlaw's method, and by the simple method of stirring the blood with a wire until a thread of fibrin became attached, was observed from time to time. In all, the patient had fifteen subcutaneous injections of sheep-serum, the total amount being 56 c.c. The coagulation times showed no improvement whatever, and if anything the symptoms were worse after treatment. Unfortunately the serum used was by no means fresh, its age varying from one to four weeks in the different injections.

(f) *Introduction of horse-serum.* This form of treatment was only given a brief trial on one case, and, as with sheep-serum, no coagulation curves were obtained. 10 c.c. of horse-serum were administered intravenously, and although previous intradermal tests had been negative, pronounced anaphylactic phenomena were observed. This was followed by no clinical improvement, but by a slight improvement in the coagulation time.

2. *Introduction of other Coagulative Elements.*

(a) *Introduction of calcium.* The administration of calcium by the mouth, which has been abandoned by practically all modern investigators, probably owed its popularity to the fact that administration is easy, and something is better than nothing. The only published case that we can find where definite improvement is claimed is that of Max Kahn (Sajous (11)), in which there was admittedly no haemophilic family history, and the blood calcium was definitely below normal,

a thing unknown in true haemophilia. We have tried prolonged administration of calcium lactate in four cases (Cases I, II, V, VI), with completely negative results.

Intravenous injection of calcium chloride in animals has been shown by Gratia (29) to produce disintegration of the platelets without thrombus formation. According to modern conceptions of haemophilia, this form of treatment might be of benefit, but as far as we know has never been tried.

(b) *Administration of haemostatic serum* (Lapenta). This is another popular form of treatment, the value of which has been, in our opinion, very much overrated. The pamphlet issued by the manufacturers states that the active ingredients are:

- (1) Prothrombin.
- (2) Thrombokinase (thromboplastic substance).
- (3) Anti-antithrombin, which in modern terminology is identical with thrombokinase.

It is a recognized fact that should thromboplastic substance (thrombokinase) be injected intravenously, as is advised with this serum, either you get intravenous clotting with instantaneous death if injected rapidly, or, if injected slowly, the production of 'negative phase' blood with *decreased* coagulability (Mellanby (24), Mills (30)). Thus the introduction of thromboplastic substance (thrombokinase) can only do harm.

We have analysed samples of the serum and found a considerable percentage of calcium to be present (12.3 and 12.5 mg. per 100 c.c. in two samples), which would ensure the transformation of the prothrombin and thromboplastic substance (thrombokinase) into thrombin. We believe this latter to be the active ingredient of hemoplastin, and, since we have found experimentally that anything less than 10 per cent. of hemoplastin in haemophilic blood *in vitro* does not hasten coagulation to any appreciable degree (Table I), it seems improbable that so small an amount as 2-4 c.c. should affect the 4-6 litres of circulating blood, where the concentration would be 0.03 to 0.1 per cent.

TABLE I.

Case.	Amount of Blood.	Amount of Haemostatic Serum.	Dilution.	Temperature.	Clotted.
	c.c.	c.c.	%		
IV	1	—	—	17° C.	6 hr. 30 min.
"	1	0.001	0.1	17° C.	6 " 40 "
"	1	0.002	0.2	17° C.	5 " 35 "
"	1	0.01	1.0	17° C.	4 " 50 "
"	1	0.02	2.0	17° C.	4 " 50 "
"	1	0.1	10.0	17° C.	3 " 40 "
"	1	0.2	20.0	17° C.	2 " 35 "
Normal	1	—	—	17° C.	0 " 13 "

We have tried the effect of hemoplastin on three cases:

(1) *Case I.* Four intravenous injections of 2 c.c. hemoplastin at 4-6-day intervals. No definite improvement in coagulation time, but followed by freedom from symptoms for three weeks. After last injection marked anaphylactic phenomena.

(2) *Case II.* Three injections of 4 c.c. hemoplastin intramuscularly at intervals of twenty-four hours. No improvement in coagulation curve. Marked pain and tenderness in buttock after last injection, probably due to haemorrhage. One injection of 4 c.c. hemoplastin intravenously, followed by marked anaphylactic phenomena. No improvement in coagulation curve.

(3) *Case VI.* Has had 2 c.c. hemoplastin intramuscularly, at intervals of two months, for two years. No clinical improvement.

Thus it would appear that hemoplastin is of little or no therapeutic value in haemophilia. Given intravenously it endangers life, owing to the risk of protein shock, and given intramuscularly we and others have found that there is a definite danger of the formation of a haematoma at the site of injection.

(c) *Administration of 'tissue fibrinogen' (Fibrinogen-Merrell).* This is another preparation which has a considerable vogue in the treatment of haemophilia, although we have not been able to find any authenticated case where definite improvement followed its use. Its active principle is admittedly thromboplastic substance (thrombokinas), so, whether administered orally or subcutaneously, it must necessarily pass through the blood-stream before distributing itself in the tissues, and must therefore expose itself to the factors described in the previous paragraph, thus rendering it either useless or harmful. Given intravenously it is a lethal preparation (30).

In Case II we gave the recommended subcutaneous dose at 12-hourly intervals, till three injections had been given. No improvement was found in the coagulation curve. In Case III we gave the recommended subcutaneous dose once. A marked local reaction resulted, with slight involvement of the glands in the axilla. No improvement was found in the coagulation curve or in the symptoms.

3. *Stimulation of Coagulation.*

(a) *Introduction of sodium citrate.* The evident success which has attended the use of this drug in other haemorrhagic diseases has led us to give it a fairly extensive trial in haemophilia. That the intravenous injection of small quantities of sodium citrate is definitely followed by a hyper-coagulability of the blood in a normal subject has been shown by Weil (35), Pickering and Hewitt (36), and others, although the actual mechanism of this improvement has never been demonstrated. It is not the actual presence of the citrate that is responsible, since this is very rapidly oxidized and removed from the tissues (Sabbatini (37), Salant and Wise (38)), but is probably something of the nature of a recalcification *in vivo* (Pickering and Hewitt (36)).

In the cases described each injection has been of 0.6 gm. sodium citrate in 20 c.c. distilled water, given intravenously.

Case V. Nine injections in all, at intervals of two weeks. No improvement in blood coagulation, but has been quite free from symptoms, and has firm belief in the benefit which has accrued from his injections.

Case III. Seven injections at 4-day intervals, followed by eight injections at weekly intervals. No improvement in coagulation, but symptoms relieved apart from bruising. On returning home from his last injection, he fractured his patella. This was followed by extensive haemorrhage into the joint and surrounding tissues, the leg being swollen and discoloured from hip to toe. With each of the first three injections the coagulation time was taken immediately before and 15 minutes after the injection, by means of placing venous blood in a test-tube at 37° C. The following figures show a definite increase in the coagulability :

	Coagulation time before injection.	After injection.
(1)	35 minutes	16 minutes
(2)	46 „	34 „
(3)	47 „	25 „

Coagulation curves, however, taken six hours later showed no improvement.

Case IV. Sixteen injections at 3-4-day intervals, followed by four at 7-day intervals. No improvement in coagulation curve. Patient states, however, that he never remembers being so free from symptoms as he has been since commencing injections. Has only had occasional slight bleedings into right elbow.

Thus it would seem that intravenous sodium citrate produces a very transient increase in the coagulability of the blood. In the three cases described this was followed by a permanent clinical improvement, but the degree of this improvement does not warrant the assumption that it was due to the injection of sodium citrate.

(b) *Administration of peptone.* This form of treatment has not yet been thoroughly investigated, but what has been done gives little hope of success (Sajous (11)). We gave Case I a series of intravenous injections of Armour's No. 2 peptone, 5 per cent., starting at 0.015 c.c. and finishing at 1.5 c.c., eleven injections, and 11.2 c.c. in all, at intervals of 3-4 days. The patient is convinced that there was no clinical improvement.

(c) *Protein shock.* In the two cases described we have been unable to confirm the work of Vines (31) and Mills (32), who claim a definite improvement after anaphylactic shock or protein sensitization.

Case I. (a) 10 c.c. horse-serum intravenously. Slight anaphylactic phenomena, followed by appearance of pronounced serum rash. No improvement in symptoms. Slight improvement in coagulation time.

(b) 4 c.c. haemostatic serum intravenously. Very marked anaphylactic phenomena. No improvement in symptoms nor coagulation time.

Case II. 4 c.c. hemostatic serum intravenously. Very marked anaphylactic phenomena. No improvement in symptoms nor coagulation time.

(d) *Administration of thymus extract.* This form of treatment is advised in many text-books, but no definite evidence has been produced to prove its utility. Case I took it by the mouth for some months with no beneficial results. The injection of thymus nucleic acid will be dealt with later.

Miscellaneous. Amongst the many other substances that have been tried with no proven success are gelatin, raw meat juice, milk, thyroid extract, ergot, adrenalin, turpentine, perchloride of iron, and practically every known styptic. Locally we have found that fresh human blood applied in cotton-wool after all useless clots have been removed is the most efficacious coagulant.

Prophylaxis. It is obvious that trauma of any sort must be strictly avoided, but apart from this we have little evidence as to what causes the exacerbations which are so typical of the disease. Case I, a well-educated and very intelligent patient, is quite certain that the use of any strong purge is very often instrumental in starting a sequence of haemorrhages. Cases III, IV, and V are equally convinced that while leading an open-air life the haemorrhagic tendency is diminished.

Suggestions as to Further Methods of Treatment.

(a) *Disintegration of platelets*, thus liberating prothrombin for coagulative purposes. Both antiplatelet serum (Bedson (33)) and intravenous calcium chloride (Gratia (29)) have been shown to disintegrate the platelets *in vivo* in animals, and as far as we know neither has been tried in haemophilia. The dangers of intravascular clotting, and the production of purpura, would have to be carefully considered.

(b) A defibrinated transfusion of the patient's own blood should be effective in cases of emergency, as has already been suggested.

(c) Thymus nucleic acid in small quantities has been shown to accelerate clotting (Pickering and Taylor (34)), and to our knowledge has never been tried in haemophilia.

Conclusions.

1. The only means by which the coagulability of haemophilic blood can be increased to any appreciable extent, and the symptoms definitely controlled, is by blood transfusion, whether it be whole blood, citrated blood, or defibrinated blood. Of these we believe the citration method to be the best.

2. This improvement lasts from five to seven days; it is the degree and not the duration of improvement which depends on the amount of blood given. We found no negative phase as was suggested by Addis.

3. A slight but transient improvement was obtained after intravenous injections of fresh human sera. Subsequent injections produced no cumulative action.

4. Hemostatic serum, sheep-serum (not fresh), horse-serum (not fresh), 'Fibrinogen-Merrell', peptone, calcium, thymus extract, and protein shock have been tried with negative results.

5. Intravenous sodium citrate has been given an extensive trial, and appears to be of some slight therapeutic value.

6. Locally we have found the most effective coagulant to be fresh human blood soaked in cotton-wool and applied after removal of all useless clots.

7. Antiplatelet serum, intravenous calcium chloride, and thymus nucleic acid are suggested as being worthy of a trial in the treatment of haemophilia.

Case Reports.

Case I. F. J. D., male, aged 34. *History.* Definite of haemophilia for three generations. Six definite cases in family. *Symptoms.* Bruises easily. Typical haemorrhage into joints, kidneys, lungs, gums, and nose. One almost fatal haemorrhage after an accident.

Case II. J. C., male, aged 20. *History.* Definite of haemophilia for one generation only. Three haemophilic brothers, one haemophilic cousin. *Symptoms.* Bruises easily. Frequent epistaxis and bleeding from gums, sometimes leading to severe anaemia. Very severe haemorrhage from trauma on three occasions, once almost fatal. No haemorrhage into joints. A comparatively mild haemophilia.

Case III. W. E., male, aged 25. *History.* Definite of haemophilia for one generation. (Previous family history not known.) Four definite cases in family, four indefinite, died in infancy. *Symptoms.* Bruises easily. Typical haemorrhages into joints, bowel, kidneys, gums, and nose. Almost fatal haemorrhage from scalp wound. Joints typically ankylosed.

Case IV. J. C., male, aged 25. *History.* First cousin of Case III. *Symptoms.* Bruises easily. Typical haemorrhages in joints, gums, and nose. Very severe haemorrhage from trauma on four occasions, once almost fatal.

Case V. J. W. S., male, aged 41. *History.* Definite of haemophilia for five generations. Twelve cases on record. *Symptoms.* Bruises easily. Typical haemorrhages into joints, kidneys, bowel, gums, and nose. Many trivial accidents followed by severe haemorrhage.

Case VI. G. M., male, aged 7. *History.* Definite of haemophilia for two generations. Five definite cases in family. *Symptoms.* Bruises easily. Typical haemorrhages into joints and gums. Almost fatal haemorrhage from scalp injury.

In conclusion, we would like to thank Dr. C. P. Stewart for kindly performing the quantitative calcium estimations.

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PROCEEDINGS OF THE ASSOCIATION OF PHYSICIANS OF GREAT BRITAIN AND IRELAND

TWENTIETH ANNUAL GENERAL MEETING

THE TWENTIETH ANNUAL GENERAL MEETING was held at Newcastle-upon-Tyne, on Friday and Saturday, May 21 and 22, 1926, in the Medical Library, Royal Victoria Infirmary.

Proceedings began at 10 a.m.

The President, Sir Humphry Rolleston, was in the chair.

The minutes of the last Annual Meeting, having been published in this Journal, were taken as read and confirmed.

The President referred to the great loss sustained by the Association since the last meeting by the death of Sir Richard Douglas Powell. A letter of condolence had been sent to his son by the President.

Election of President. Sir David Drummond was elected President for 1926-7. On his election he took the chair and expressed the thanks of the Association to the retiring President, Sir Humphry Rolleston, for his services during the past year.

Election of Honorary Members. The following Honorary Members were elected: Sir Humphry Rolleston, the retiring President, and Sir William Hale-White. The President referred to the past services of Sir William Hale-White, who had been Treasurer since the foundation of the Association, and proposed a very hearty vote of thanks, which was passed unanimously.

The election of Officers, members of the Executive Committee, and new members followed.

Treasurer. Dr. H. Morley Fletcher.

Secretary. Dr. H. Letheby Tidy.

Members for England:

Professor F. R. Fraser.
Professor J. W. McNee.
Professor F. Craven Moore.
Dr. F. J. Nattrass.
Dr. J. A. Ryle.
Dr. R. A. Veale.

Members for Scotland:

Dr. J. B. M. Anderson.
Professor A. Patrick.
Dr. W. T. Ritchie.

Members for Ireland:

Dr. J. S. Morrow.
Professor W. W. D. Thomson.
Dr. W. A. Winter.

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New Members.

Alexander Greig ANDERSON, M.D., Assist. Phys., Aberdeen Royal Infirmary.

Geoffrey BOURNE, M.D., Assistant to Medical Professorial Unit, St. Bartholomew's Hospital.

Foster COATES, M.D., Physician, Royal Victoria Hospital, Belfast.

John Norman CRUICKSHANK, M.D., Senior Assistant, Muirhead Chair of Medicine, Glasgow.

Harold GARDINER-HILL, M.B., attached to Medical Unit, St. Thomas's Hospital.

Thomas Lionel HARDY, M.D., Assist. Phys., General Hospital, Birmingham.

William Geoffrey HARVEY, M.D., Physician, Adelaide Hospital, Dublin.

Edward MELLANBY, M.D., F.R.S., Physician, Royal Infirmary, Sheffield.

James Aubrey TORRENS, M.D., Physician, St. George's Hospital.

Charles Wilfred VINING, M.D., Physician, Leeds General Infirmary.

The President expressed the warm thanks of the Association to Dr. Morley Fletcher for his services as Secretary since 1920, and their pleasure that he was undertaking the Treasurership.

Presentation of Treasurer's Accounts. Sir William Hale-White presented his annual report, which was adopted. This showed a balance of £169.

Annual General Meeting in 1927. A letter was read from Dr. McKisack, inviting the Association to meet at Belfast in 1927. The invitation was cordially accepted.

In the absence of Professor Craven Moore, Dr. Morley Fletcher moved the resolution standing in his name, 'That the Association regrets the cessation of publication of *Medical Science and Abstracts*, and expresses the hope that the Medical Research Council may consider the reissue of this valuable publication'. This was carried unanimously, and the Secretary was directed to forward a copy of the resolution to the Secretary of the Medical Research Council.

Dr. Tyson raised the question of the possibility of holding a meeting in America. Dr. Morley Fletcher pointed out that, according to Rule 13, meetings must be held in the British Isles. The matter was dropped.

SCIENTIFIC BUSINESS.

Friday Morning, May 21.

1. Professor A. Ellis on 'Iodine and Exophthalmic Goitre'. He described the results produced on the metabolism and general condition by the administration of iodine.

2. Dr. A. G. Yates on 'Lipiodol in the diagnosis of Cord Lesions'. He showed lantern slides illustrating the results obtained by radiography after cisternal injection of lipiodol. It was important to take the first radiogram within a few minutes of the injection, as if the block was incomplete the lipiodol quickly began to leak through. Further slides illustrated partial obstruction by meningeal adhesions. Here the lipiodol was not held up *en masse*, but was fragmented and often appeared as a network.

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Dr. Hurst advised screening on a table which could be tipped up or down.

Drs. Starling, Riddoch, and Symonds also joined in the discussion.

3. Dr. F. G. Chandler on 'The uses and limitations of Lipiodol Injections in the diagnosis of Pulmonary Disease'. Lantern slides were exhibited illustrating the pictures obtained after tracheal injection of lipiodol in normal subjects, and with various diseases of the lungs. Bronchiectasis gives a distinctive picture, but lipiodol does not enter a lung abscess and rarely enters a tuberculous cavity. He used injections of 18 to 20 c.c.

Dr. Findlay stated that he had never seen lipiodol enter a tuberculous cavity.

Dr. Beattie and Dr. Morley Fletcher joined in the discussion.

4. Dr. Ivor J. Davies gave a communication on 'Atypical Tabes'. He described clinical variations of tabes, and stated that atypical forms appeared now to be common. He laid stress on the type of pain in tabes and on the occurrence of restlessness as a guide to diagnosis.

Several members discussed the communication, and quoted cases in which abdominal operations had been performed in tabes owing to erroneous diagnoses.

5. Dr. R. L. Mackenzie Wallis on 'Hepatic Insufficiency Tests in Encephalitis Lethargica and allied Nervous Diseases'. He had employed the laevulose, lipase, and Van den Bergh's tests. Evidence of hepatic insufficiency was found in nearly all cases of acute encephalitis lethargica, in most cases of paralysis agitans, and in some doubtful cases of encephalitis lethargica.

Dr. Spence stated that he had come to the conclusion that the laevulose test alone is of little value, as the information as to hepatic insufficiency which it affords can be deduced from the clinical condition.

Dr. Mackenzie Wallis, in reply, referred to the value of the laevulose test in salvarsan poisoning.

6. Dr. F. Parkes Weber described a 'Case of Primary Subarachnoid Haemorrhage simulating Encephalitis Lethargica'. The condition on admission to hospital suggested encephalitis lethargica, but examination of the cerebro-spinal fluid proved the case to be one of subarachnoid haemorrhage. The patient had suffered all her life from attacks of migraine. The probable explanation of the haemorrhage was a rupture of a small aneurysm at the base of the brain.

Dr. Symonds agreed with this explanation.

Dr. Riddoch laid emphasis on the occurrence of headache as the usual precursor of subarachnoid haemorrhage.

Dr. Parkes Weber, in reply, expressed the opinion that the migraine was not due to the aneurysm.

2-3 p.m.

1. Demonstration of clinical cases (54) at the Royal Victoria Infirmary.

2. Exhibition of pathological specimens, including a unique specimen of malakoplakia of the kidneys and bladder.

3. A collection of books and prints lent by Mr. F. C. Pybus, including Harvey's own copy of *De Generatione*.

Friday Afternoon. 3 p.m.

1. Dr. H. F. Moore recorded 'Some Observations on Hypocalcaemia'. Penfold had shown, first that free hydrochloric acid renders calcium solvent and absorbable, and secondly that when the stomach contents are neutral, insoluble calcium is found which may be rendered absorbable by neutral fat. In cases of gastric achlorhydria Dr. Moore found that the calcium content of the blood was usually normal, but occasionally deficient.

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2. Dr. J. C. Spence on 'Renal Dwarfism—the relation of the renal condition to the bone deformities'. He had recently studied five cases. The bone changes might be (1) complete cessation of growth, (2) rachitic changes at the epiphyses, or (3) osteoporosis, or a combination of these. The kidney lesion preceded the bone changes, and in most cases was chronic nephritis of the 'small white kidney' type, with marked azotaemic retention, and ending in sudden uraemia. Vascular changes were often absent. In one of his cases the chronic nephritis had been present for at least thirteen years without rise of blood-pressure.

Four of his cases had frequent attacks of tetany. The blood showed a variable but constant calcium disturbance, with reduction of the serum calcium as low as 7 mg. per 100 c.c. He believed that the bone changes were due to a disturbance of the normal proportions of calcium to phosphorus in the blood and tissue fluids as a result of the azotaemic kidney condition. In the presence of this disharmony, normal bone growth and bone formation were impossible.

Dr. Morley Fletcher inquired as to the nature of the renal changes. He believed that they commenced very early, possibly *in utero*.

Dr. L. G. Parsons and Dr. Patterson had seen similar cases improve with light treatment.

Several other members joined in the discussion.

Dr. Spence, in reply, accepted the view that the renal changes were congenital in origin.

3. Dr. A. F. Hurst on 'The Diagnosis and Treatment of Chronic Gastritis'. He stated that the only reliable criterion for diagnosis was the presence of mucus in each fraction of a test meal. Microscopical examination was of no value. The common causes were alcohol, oral and pharyngeal sepsis, and acute food poisoning. In most cases achlorhydria was present, but if the test meal were repeated after preliminary lavage, free acid appeared, unless atrophic changes had developed, so that true achylia was produced. Cases of achlorhydria could now be classified as (1) achlorhydria due to gastritis, in which free acid appeared after lavage; (2) achylia due to gastritis, in which mucus was present in each fraction; (3) constitutional achylia with no mucus, or with mucus due to secondary gastritis. Treatment consists in removal of the cause, lavage of the stomach when fasting in the morning with hydrogen peroxide (1 in 10) to dislodge the mucus, and then with plain water, and the administration of large doses of hydrochloric acid in the achylic cases.

4. Dr. H. L. Tidy on 'Blood Changes due to the Haemorrhagic Diathesis'. He described the numerous forms of blood and bone-marrow change which may result from the haemorrhages due to the haemorrhagic diathesis, the essential cause for which was regarded as an increased permeability of the capillary endothelium. He considered that the various types of primary purpura which have been described under such titles as 'purpura haemorrhagica', 'purpura rheumatica', and 'essential thrombopenia' were results of the haemorrhagic diathesis. The question of splenectomy should be considered in every case, the decision being based principally on the clinical condition.

The term 'angio-staxis' was suggested for the entire group.

Dr. Thursfield and Dr. Sutherland did not agree with the opinions expressed.

5. Dr. A. G. Gibson recorded some observations on a case of Aplastic Anaemia. A child, aged 11 years, came under observation for asthenia, a purpuric eruption, and a blood-count of R.B.C. 1,990,000 per c.mm.; W.B.C. 4,850 per c.mm.; Hb. 42 per cent.; colour index 1.06; and a differential count of 87 per cent. lymphocytes and 12 per cent. polymorphs. There were no nucleated red cells. The diagnosis of aplastic anaemia was made. She was given altogether six blood transfusions at increasingly short intervals for twenty months, at the end of which her condition was almost hopeless. She was then put on daily 5-minim doses of adrenalin chloride subcutaneously, from which time, during a period of sixteen months, she had made a gradual but uninterrupted clinical recovery, and the haemorrhages had ceased. The

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blood, however, still retained some features of aplastic anaemia—R.B.C. 3,820,000 per c.mm.; W.B.C. 3,120 per c.mm.; Hb. 72 per cent.; colour index 0.84. Differential count:—polymorphs 33 per cent.; lymphocytes 49.5 per cent. Nucleated red cells had been present subsequent to treatment by adrenalin.

Dr. C. Leyton, Professor Murray, Dr. Thursfield, and Dr. Tidy discussed this communication.

6. Dr. J. H. M. Campbell and Dr. E. P. Poulton on 'The twofold respiratory response to exercise in Chronic Bronchitis and the results of Oxygen Treatment, with a note on a case of Myocardial Degeneration'. The type of response depended on the presence or absence of an asthmatic factor.

7. Dr. R. Hilton (introduced) on 'A Comparison of Methods of Oxygen Administration'. The comparison was based on analyses of oxygen in the alveolar air. The most efficient method was a close-fitting mask over the nose and mouth. No effect was produced by administration through a large glass funnel held 10 cm. from the mouth. Intermediate results were obtained with a funnel held close over the mouth and nose, with a nasal catheter and with a mask over the mouth only.

8. Dr. G. A. Allan described 'A case of simple paroxysmal Tachycardia of Ventricular Origin, exhibiting retrograde Conduction with Partial Heart-block'. The symptoms dated back for fourteen years. The ventricular rate during paroxysms varied between 230 and 270, and with the more prolonged attacks there was loss of consciousness and twitching of the muscles of arms and face. Recorded attacks lasted between 6 and 23 seconds. There was retrograde stimulation of the auricle, with 2-1 partial heart-block, the auricular rate being half that of the ventricle. When the heart was beating quietly no obvious abnormality could be detected by physical examination, X-rays, or electro-cardiograph.

Dr. Ritchie expressed the opinion that compression of the vagus, while effective in auricular tachycardia, was useless in the ventricular form.

The Annual Dinner was held at the Central Station Hotel at 7.30 p.m. One hundred and two members and guests were present. The President, Sir David Drummond, was in the chair. The official guests included the Lord Mayor of Newcastle, the Dean of Durham, and Mr. Hunter Blair, of the Newcastle Society of Antiquaries.

Saturday Morning. 10 a.m.

1. Dr. A. E. Naish on 'Abdominal Pain in Acute Rheumatism'. He described three cases in which the abdomen has been opened during an attack of acute rheumatism on account of urgent abdominal symptoms. In all three there was evidence of acute peritonitis with turbid, blood-stained fluid and oedema of the peritoneum. In all these cases the appendix appeared to be normal. The cause of the commonly occurring abdominal pain in the acute rheumatism of childhood was discussed.

Sir William Hale-White said that forty years ago the possibility of rheumatic appendicitis was accepted.

Drs. Parkes Weber, Sutherland, and Starling also suggested that the condition was appendicitis.

Dr. Naish, in reply, pointed out that the appendix at operation was normal.

2. Dr. Abercrombie described 'Four cases of Rhumatisme Tuberculeux Ankylosant'. All were adult subjects of pulmonary tuberculosis. The cases resembled one another closely, exhibiting a chronic arthritis, with a strong tendency to insidious ankylosis. Pain was of only moderate grade; swelling was slight; no effusion into the joints was observed; and the X-ray examination of the bones was normal. The shoulder-joint was specially liable to be affected. The prognosis with regard to life was unexpectedly good. The cases were first seen in 1923; three were still living and were improving. The English name of 'toxic tuberculous arthritis' was suggested.

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Dr. Gibson stated that he had cut out a specimen from a similar joint and found tuberculous nodules.

Dr. Poulton, Dr. Beattie, and Dr. Parkes Weber also discussed this communication.

3 and 4. Dr. Devereux Forrest (introduced), on behalf of Lord Dawson and Dr. Hutchison, described two cases of Lymphadenoma.

In the first case the glandular swelling was first noticed eight years ago. For four years the patient had complained of pain in the lower lumbar vertebrae, and lately in the upper extremity. On admission to hospital, three and a half months ago, he gave the picture of amyotrophic lateral sclerosis. Radiographs showed partial destruction of the second lumbar vertebra.

In Dr. Hutchison's case the enlargement of the glands was noticed about four years previously, and improved under treatment. In July 1925 the patient complained of pain and weakness in the left leg, and was admitted to hospital in September. The glandular enlargement was slight. In October he rapidly developed complete paraplegia, with double extensor response. In six weeks this entirely passed away. The general condition became worse, and the patient died in January 1926.

At autopsy there was widespread lymphadenomatous involvement throughout the body, but no evidence of involvement of the vertebrae or cord. Microscopical examination showed definite degeneration of the posterior columns and some doubtful changes in the region of the crossed pyramidal tracts.

Dr. Hutchison mentioned a case in which paraplegia occurred with each Pel-Ebstein rise of temperature.

Dr. Buzzard described the autopsy of a case of lymphadenoma with paraplegia which suggested that the lesion was due to interference with the vascular supply of the cord.

Professor Murray, Dr. Symonds, and Dr. Parkes Weber also spoke.

Dr. Hutchison, in reply, accepted Dr. Buzzard's explanation of interference with the vascular supply.

5. Dr. C. P. Symonds on 'An unusual type of Febrile Illness with involvement of the Nervous System'. During the past year he had seen four cases resembling one another, but not conforming with any recognized clinical type.

The main features were an initial period of fever without physical signs lasting five to ten days. This was followed by nervous symptoms, including loss of deep reflexes, signs of meningitis, epileptic fits, and, in each of the three cases in which the cerebro-spinal fluid had been examined, a high lymphocytosis. The acute phase of the illness with fever lasted from three to four weeks, and recovery in all cases was complete. Clinically these cases were distinct from encephalitis lethargica.

Dr. Langdon Brown had seen several similar cases. In an autopsy on a fatal case the findings suggested encephalitis lethargica.

Dr. Wilkinson saw four attacks in one patient.

Dr. Yates and Dr. Tidy suggested that the condition was Quincke's serous meningitis.

Dr. Symonds, in reply, said that he did not think the condition was encephalitis lethargica. There was no evidence supporting the occurrence of serous meningitis, and he could express no opinion on it.

6. Dr. R. S. Allison (introduced) on 'Sugar Tolerance in Obesity'. The communication was based on sugar tolerance tests on twelve cases of overweight whose urine was sugar free, and eight cases who had glycosuria.

The results showed that many obese persons displayed a definite diabetic tendency, which was only revealed by the sugar tolerance test. After reduction of weight the sugar tolerance test gave a normal result.

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7. Dr. O. Leyton on 'Does the Pancreas regenerate in Diabetes Mellitus when correctly treated with Insulin?' He was of opinion that the pancreas recovers if rested sufficiently.

Dr. Graham did not believe that the cells in the pancreas could increase.

Several other members joined in the discussion.

8. Dr. J. Stacey Wilson on 'Carbolic Saturation as an effective means of treating certain Streptococcal Blood Infections'. Satisfactory results might be expected from the administration of large doses of sulpho-carbolate of soda.

2-3 p.m.

Demonstration of Clinical Cases, Pathological Specimens, Medical Books, and Portraits in the Royal Victoria Infirmary.

Saturday Afternoon. 3 p.m.

1. Dr. G. Evans, with Dr. T. H. Green (introduced), on 'Electro-cardiograph Changes associated with raised Blood-pressure'. Cases of chronic high blood-pressure were classified in various groups and the electro-cardiographs described.

2. Dr. S. W. Patterson, with Dr. W. H. Grace (introduced), on 'Observations on the Results of the Wassermann Reaction, including a series of 500 consecutive cases'. The subjects were upper and middle-class patients. Sixteen were positive (3.3 per cent.), and of these eleven (2.2 per cent.) were not suspected from history or clinical evidence. Of the eleven unsuspected cases, five had symptoms of gastric or duodenal ulcer, one had nerve deafness and cystitis, one a recurrent periarticular inflammation, and four had evidence of cardio-vascular affection.

3. Dr. C. H. Andrewes (introduced) described 'A case of Septicaemia due to Morgan's No. 1 Bacillus'. A girl aged 12 years was taken ill with headache, drowsiness, and stiffness of the neck, followed by rigors. There was moderate diarrhoea from the third to the fifth day of her illness only. She gave a past history of aural discharge, which had dried up a month before. On admission she had haematuria. Later she developed pneumonia and a spontaneous pneumothorax. Morgan's No. 1 bacillus was recovered from the blood culture, urine, stools, and pleural fluid. She died on the twenty-fifth day of her illness. Autopsy showed pulmonary abscesses, an infected clot in the inferior vena cava, a lateral sinus thrombosis, and otitis media. Morgan's No. 1 bacillus was isolated, along with other organisms, from the lateral sinus, heart's blood, and vena cava. No intestinal lesions were found.

4. Dr. G. Hall gave a history of very short fatal illness in several children of one family. In a family of six children there had occurred at various times three deaths after very short preliminary illness of no special characteristics. No results of autopsy were available. The remaining children seemed perfectly healthy.

Sir David Drummond suggested lymphatism as the cause.

Dr. Beattie suggested the possibility of anaphylaxis.

Dr. Hall, in reply, stated that one boy had tonsillectomy performed under a general anaesthetic without trouble.

5. Dr. W. E. Hume discussed 'The action of Adrenalin Chloride on the Human Heart'.